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BPC073TO THE ASSISTANT COMMISSIONER FOR PATENTS

Transmitted herewith for filing under 35 U.S.C. 111 and 37 C.F.R. 1.53 is the patent application of:

Michael Chorev, Zheng Xin Dong and Michael RosenblattFor: **PTH2 Receptor Selective Compounds**

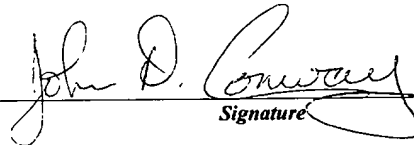
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Applicant(s):			BPC073
Serial No. To be assigned	Filing Date Filed herewith	Examiner To be assigned	Group Art Unit To be assigned
Invention: PTH2 Receptor Selective Compounds			
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Patent
BPC073

**NON-PROVISIONAL APPLICATION
UNDER 37 CFR 1.53(b)(1)**

TITLE: PTH2 RECEPTOR SELECTIVE COMPOUNDS
APPLICANTS: M. CHOREV, Z. X. DONG AND M. ROSENBLATT

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PTH2 RECEPTOR SELECTIVE COMPOUNDS

Statement as to Government Funding

5 This invention was supported in part by Government funding, NIDDK Research Grant DK-4790, and the Government, therefore, may have certain rights in the invention.

Background of the Art

10 This invention relates to a series of PTH and PTHrP analogues that selectively bind to PTH2 receptors and as such may be useful in treating abnormal CNS functions; abnormal pancreatic functions; divergence from normal mineral metabolism and homeostasis; male infertility; regulation of abnormal blood pressure; and hypothalamic disease, to name a few potential uses.

15 An alternate human parathyroid hormone (PTH) receptor, designated as PTH2 receptor, has been identified in rat and human brain. This receptor is selectively activated by PTH-(1-34), but not PTH-related protein PTHrP-(1-34), which has the same calcium-mobilizing activities as PTH-(1-34). Both PTH and PTHrP share a common G protein-coupled receptor, termed the PTH/PTHrP receptor. The PTH2 receptor is localized predominantly in the brain and pancreas, in contrast to PTH/PTHrP receptor, which is primarily localized in bone and the kidney, the principal target tissue for PTH action.

20 Parathyroid hormone (PTH) is the principal physiological regulator of calcium levels in the blood (Chorev, M., Rosenblatt, M., 1994, Structure function analysis of parathyroid hormone and parathyroid hormone-related protein, Bilezikian, J.P., Marcus, R., Levine, M., (eds) The Parathyroids: Basic and Clinical Concepts. Raven Press, New York, pp 139-156; Juppner, H., et al., 1991, Science, 254:1024-1026; and Martin, T.J., et al., 1991, Crit. Rev. Biochem.

25 Mol. Biol. 26:377-395). PTH-related protein (PTHrP) was originally identified as the agent responsible for the paraneoplastic syndrome of humoral hypercalcemia of malignancy (Suva, L.J., et al., 1987, Science, 237:893-896 and Orloff, J.J., et al., 1994, Endocrinol. Rev. 15:40-60). PTH and PTHrP are products of distinct, yet evolutionary-related genes. PTH and PTHrP show sequence similarities only in the N-terminal 13 amino acids, 8 of

30 which are identical (Abou-Samra AB, et al., 1992, Proc. Natl. Sci. Acad. USA, 89 2732-2736). However, the expression pattern and physiological role of these two molecules are remarkably different. PTH has a highly restricted pattern of expression and acts as a classical endocrine hormone, whereas PTHrP is expressed in a wide variety of normal

tissues and functions in a predominantly autocrine/paracrine fashion (Urena, P., et al., 1993, *Endocrinology*, 133:617-623; Lee, K., et al., 1995, *Endocrinology*, 136:453-463; and Martin, T.J., et al., 1995, *Miner. Electrolyte Metab.*, 21:123-128). More recently, PTHrP has been shown to play a fundamental role in embryonic differentiation of bone and cartilage development.

PTH and PTHrP exert their wide-ranging effects via a common receptor located on the surface of target cells (Juppner, H., et al., 1988, *J. Biol. Chem.*, 263:1071-1078, Shigeno, C., et al., 1988, *J. Biol. Chem.*, 263:18369-18377). The PTH/PTHrP receptor is a member of a subfamily of G protein-coupled receptor superfamily, which includes the receptors for glucagon, growth hormone-releasing hormone (GHRH), vasoactive intestinal peptide (VIP), glucagon-like peptide 1 (GLP-1), gastric inhibitory polypeptide (GIP), secretin, pituitary adenylate cyclase-activating polypeptide (PACAP), calcitonin, and corticotropin-releasing factor (CRF) (Segre, G., et al., 1993, *Trends Endocrinol. Metab.* 4:309-314). The PTH/PTHrP receptor recognizes the N-terminal 1-34 regions of both ligands (Schipani, E., et al., 1993, *Endocrinology*, 132:2157-2165) and is particularly abundant in classical PTH target tissues such as bone and kidney (Urena, P., et al., 1993 *Endocrinology*, 133:35-38). Ligand binding to the PTH/PTHrP receptor can activate at least two signaling pathways; the adenylyl cyclase-cAMP-protein kinase A pathway (Partridge, NC, et al., 1981, *Endocrinology* 108 220-225), and the inositol trisphosphate-cytosolic calcium-protein kinase C pathway (Abou-Samra, A-B., et al., 1989, *Endocrinology* 124:1107-1113).

An homologous receptor for PTH, designated the PTH2 receptor, has been identified and partially characterized (Behar, V., et al., 1996, *Endocrinology*, 137 2748-2757; Gardella, T.J., et al., 1996, *The J. Biol. Chem.*, 271:19888-19893; Behar, V. et al., 1996, *Endocrinology*, 137:4217-4224; and Usdin, T.B., et al., 1997, *Endocrinology*, 138:831-834). Amongst the seven transmembrane G protein-coupled receptors, the PTH2 receptor is most similar in sequence to the PTH/PTHrP receptor (51% of the amino acid sequence identify). Interestingly, PTH2 receptor mRNA is not detected in bone or osteosarcoma cell lines, but is expressed in a number of tissues including the exocrine pancreas, lung, heart, vasculature, and epididymis, and is most abundant in the brain (Usdin, T.B., et al., 1996, *Endocrinology*, 137:4285-4297). Unlike the PTH/PTHrP receptor, which binds and is activated by both PTH-(1-34) and PTHrP-(1-34), the PTH2 receptor binds and is activated only by PTH-(1-34). PTHrP(7-34) was found to recognize PTH2 receptor and weakly activate it. Moreover, His⁵ in PTHrP was identified as the "specificity

switch" for the PTH2 receptor. Swapping a single amino acid, His⁵ from PTHrP, with Ile⁵ from PTH, resulted in a PTHrP analogue, Ile⁵-PTHrP-(1-34)NH₂, which acts as a PTH-2 receptor agonist. Hence, the single amino acid switch converts inactive PTHrP into a potent PTH2 receptor agonist. But while [Ile⁵]PTHrP binds and activates both receptors, PTH/PTHrP and PTH2, it is not a selective PTH2 agonist. In transient heterologous (with respect to species) expression systems, others have found an additional contribution to hPTH2 receptor selectivity by Trp²³ (Gardella et al., JBC 1996, 271:19888-19893). Like the PTH/PTHrP receptor, PTH binding leads to PTH2 receptor-mediated activation of both cAMP and [Ca²⁺] intracellular signaling pathways.

The physiological function of the PTH2 receptor because of its high abundance and distribution in the brain suggests that it may act as a neurotransmitter receptor. PTH has been found in the central nervous system (CNS) (Harvey, S., et al., 1993, J. Endocrinol. 139:353-361), therefore, it is possible that endogenous PTH2 receptor specific ligands, which are distinct from PTH, do exist in the CNS. Recently, Usdin reported the isolation of "PTH2 receptor binding activity" from the hypothalamus which was immunologically distinct from PTH.

PCT Application Number PCT/US97/13360, published as PCT Publication Number WO 98/04591, discloses the use of certain PTHrP analogs which are PTH2 receptor agonists or antagonists

U.S. Patent No. 5,723,577, issued March 3, 1998, discloses certain PTH and PTHrP analogues. U.S. Application Nos. 08/779,768 and 08/813,534, filed January 7, 1997 and March 7, 1997, respectively, disclose further PTH and PTHrP analogs.

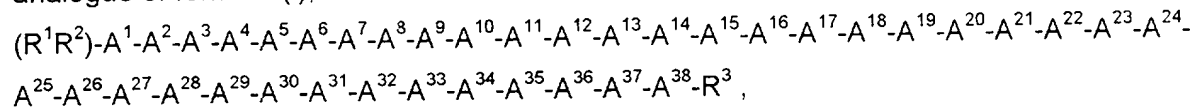
The development of specific ligands which activate the PTH2 receptor but not the PTH/PTHrP receptor, would be highly useful in defining the physiological roles of the PTH2 receptor and its potential involvement in certain pathological states. We have discovered a series of PTH2 receptor-selective PTH analogues which interact selectively with the human PTH2 receptor and are practically devoid of PTH/PTHrP receptor interaction. The compounds of the present invention are not only selective toward a receptor subtype but also signal specifically through the stimulation of [Ca²⁺]_i transients. Therefore, the compounds of the present invention are receptor subtype and signaling pathway selective.

Summary of the Invention

In one aspect, this invention provides a PTH analogue or a truncated PTH analogue or a pharmaceutically acceptable salt thereof that selectively binds to the PTH2 receptor. A

preferred PTH analogue or a truncated PTH analogue or a pharmaceutically acceptable salt thereof is where the analogue is a selective PTH2 receptor agonist. Another preferred PTH analogue or a truncated PTH analogue or a pharmaceutically acceptable salt thereof is where the analogue is a selective PTH2 receptor antagonist.

- 5 A more preferred PTH analogue that selectively binds to the PTH2 receptor is an analogue of formula (I),



(I)

- 10 or a pharmaceutically-acceptable salt thereof wherein

A¹ is a hydrophilic or a lipophilic amino acid;

A² is a lipophilic amino acid;

A³ is a hydrophilic or a lipophilic amino acid;

A⁴ is a hydrophilic amino acid.

- 15 A⁵ is a hydrophilic or a lipophilic amino acid;

A⁶ is a hydrophilic amino acid or is deleted;

A⁷ is a hydrophilic or a lipophilic amino acid or is deleted;

A⁸ is a lipophilic amino acid or is deleted;

A⁹ is a hydrophilic amino acid or is deleted;

- 20 A¹⁰ is a hydrophilic amino acid or is deleted;

A¹¹ is a hydrophilic or a lipophilic amino acid or is deleted;

A¹² is a hydrophilic or a lipophilic amino acid or is deleted;

A¹³ is a hydrophilic amino acid;

A¹⁴ is a hydrophilic amino acid or is deleted;

- 25 A¹⁵ is a lipophilic amino acid or is deleted;

A¹⁶ is a hydrophilic or a lipophilic amino acid or is deleted;

A¹⁷ is a hydrophilic or a lipophilic amino acid or is deleted;

A¹⁸ is a lipophilic amino acid or is deleted;

A¹⁹ is a hydrophilic or a lipophilic amino acid or is deleted;

- 30 A²⁰ is a hydrophilic amino acid or is deleted;

A²¹ is a hydrophilic or a lipophilic amino acid or is deleted;

A²² is a lipophilic or a hydrophilic amino acid or is deleted;

A²³ is a hydrophilic or a lipophilic amino acid;

A²⁴ is a hydrophilic or a lipophilic amino acid;

A²⁵ is a hydrophilic amino acid;

A²⁶ is a hydrophilic amino acid;

A²⁷ is a lipophilic or a hydrophilic amino acid;

5 A²⁸ is a lipophilic amino acid;

A²⁹ is a lipophilic or a hydrophilic amino acid;

A³⁰ is a hydrophilic or a lipophilic amino acid;

A³¹ is a lipophilic or a hydrophilic amino acid or is deleted;

A³² is a hydrophilic amino acid or is deleted;

10 A³³ is a hydrophilic amino acid or is deleted;

A³⁴ is a lipophilic amino acid or is deleted;

A³⁵ is a lipophilic amino acid or is deleted;

A³⁶ is a lipophilic or a hydrophilic amino acid or is deleted;

A³⁷ is a lipophilic amino acid or is deleted;

15 A³⁸ is a lipophilic or a hydrophilic amino acid or is deleted;

R¹ and R² are each independently selected from the group consisting of H, (C₁₋₃₀)alkyl, (C₂₋₃₀)alkenyl, phenyl-(C₁₋₃₀)alkyl, naphthyl(C₁₋₃₀)alkyl, hydroxy(C₁₋₃₀)alkyl, hydroxy(C₂₋₃₀)alkenyl, hydroxy-phenyl(C₁₋₃₀)alkyl or hydroxy-naphthyl(C₁₋₃₀)alkyl;

20 or one of R¹ or R² is COE¹ where E¹ is (C₁₋₃₀)alkyl, (C₂₋₃₀)alkenyl, phenyl(C₁₋₃₀)alkyl, naphthyl(C₁₋₃₀)alkyl, hydroxy(C₁₋₃₀)alkyl, hydroxy(C₂₋₃₀)alkenyl, hydroxy-phenyl(C₁₋₃₀)alkyl or hydroxy-naphthyl(C₁₋₃₀)alkyl; and

R³ is OH, NH₂, (C₁₋₃₀)alkoxy or NH-Y-CH₂-Z, where Y is a (C₁₋₃₀) hydrocarbon moiety and Z is CO₂H or CONH₂;

provided that the compound is not PTH(1-34)R³, PTH(1-35)R³, PTH(1-36)R³, PTH(1-37)R³,

25 or PTH(1-38)R³.

Another preferred group of PTH analogues that selectively binds to the PTH2 receptor is an analogue of formula (II),

(R¹R²)-A¹-A²-A³-A⁴-A⁵-A⁶-A⁷-A⁸-A⁹-A¹⁰-A¹¹-A¹²-A¹³-A¹⁴-A¹⁵-A¹⁶-A¹⁷-A¹⁸-A¹⁹-A²⁰-A²¹-A²²-A²³-A²⁴-
A²⁵-A²⁶-A²⁷-A²⁸-A²⁹-A³⁰-A³¹-A³²-A³³-A³⁴-A³⁵-A³⁶-A³⁷-A³⁸-R³,

30 (II)

or a pharmaceutically-acceptable salt thereof wherein

A¹ is Ser, Ala, Dap, Thr, Aib or is deleted;

A² is Val, Leu, Ile, Phe, Nle, β-Nal, Aib, p-X-Phe, Acc, Cha, Met or is deleted;

A⁴ is Glu, Asp or is deleted;

A⁶ is Gln, a hydrophilic amino acid or is deleted;

A⁸ is Met, Nva, Leu, Val, Ile, Cha, Acc, Nle, p-X-Phe, Phe, β-Nal, Bpa, a lipophilic amino acid or is deleted;

10 A¹⁰ is Asn, a hydrophilic amino acid or is deleted;

A¹² is Gly, Acc, Aib, or is deleted;

15 A¹⁴ is His or is deleted;

A¹⁶ is Ser, Asn, Ala, Aib or is deleted;

A¹⁸ is Met, Nva, Leu, Val, Ile, Nle, p-X-Phe, Phe, β-Nal, Acc, Cha, Aib or is deleted;

A²⁰ is Arg, Lys, HN-CH((CH₂)_nNH-R⁴)-C(O) or is deleted;

A²² is Acc, Aib, Glu or is deleted;

25 A²⁴ is Leu, Acc, Ile, Val, Phe, β-Nal, Nle, Aib, p-X-Phe or Cha;

A²⁵ is Arg, Lys or HN-CH((CH₂)_nNH-R⁴)-C(O);

A^{26} is Arg, Lys or $\text{HN-CH}((\text{CH}_2)_n\text{NH-R}^4)\text{-C(O)}$;

30 A²⁸ is Leu, Acc, Cha, Ile, Val, Phe, Nle, β -Nal, Aib or p-X-Phe;

A²⁹ is Gln, Acc or Aib;

A³⁰ is Asp, Lys, Arg or is deleted;

A³¹ is Val, Leu, Nle, Acc, Cha, Phe, Ile, β-Nal Aib, p-X-Phe or is deleted;

A³² is His or is deleted;

A³³ is Asn or is deleted;

A³⁴ is Phe, Tyr, Amp, Aib, β-Nal, Cha, Nle, Leu, Ile, Acc, p-X-Phe or is deleted;

5 A³⁵ is Val, Leu, Nle, Acc, Cha, Phe, Ile, β-Nal Aib, p-X-Phe or is deleted;

A³⁶ is Ala, Val, Aib, Acc, Nva, Abu or is deleted;

A³⁷ is Leu, Val, Nle, Ile, Cha, β-Nal, Trp, Pal, Acc, Phe, p-X-Phe, a lipophilic amino acid, or is deleted;

A³⁸ is Gly, Acc, Aib, or is deleted;

10 where X for each occurrence is independently selected from the group consisting of OH, a halo and CH₃;

R¹ and R² are each independently selected from the group consisting of H, (C₁₋₃₀)alkyl, (C₂₋₃₀)alkenyl, phenyl-(C₁₋₃₀)alkyl, naphthyl(C₁₋₃₀)alkyl, hydroxy(C₁₋₃₀)alkyl, hydroxy(C₂₋₃₀)alkenyl, hydroxy-phenyl(C₁₋₃₀)alkyl or hydroxy-naphthyl(C₁₋₃₀)alkyl;

15 or one of R¹ or R² is COE¹ where E¹ is (C₁₋₃₀)alkyl, (C₂₋₃₀)alkenyl, phenyl(C₁₋₃₀)alkyl, naphthyl(C₁₋₃₀)alkyl, hydroxy(C₁₋₃₀)alkyl, hydroxy(C₂₋₃₀)alkenyl, hydroxy-phenyl(C₁₋₃₀)alkyl or hydroxy-naphthyl(C₁₋₃₀)alkyl;

R³ is OH, NH₂, (C₁₋₃₀)alkoxy or NH-Y-CH₂-Z, where Y is a (C₁₋₃₀) hydrocarbon moiety and Z is CO₂H or CONH₂;

20 n for each occurrence is independently an integer from 1 to 5; and

R⁴ for each occurrence is independently (C_{1-C30})alkyl, (C_{1-C30})acyl or -C((NH)(NH₂));

provided that the compound is not PTH(1-34)R³, PTH(1-35)R³, PTH(1-36)R³, PTH(1-37)R³, or PTH(1-38)R³.

In another aspect, this invention provides a PTHrP analogue that selectively binds to the PTH2 receptor of the formula (IV),

(R¹R²)-A¹-A²-A³-A⁴-A⁵-A⁶-A⁷-A⁸-A⁹-A¹⁰-A¹¹-A¹²-A¹³-A¹⁴-A¹⁵-A¹⁶-A¹⁷-A¹⁸-A¹⁹-A²⁰-A²¹-A²²-A²³-A²⁴-A²⁵-A²⁶-A²⁷-A²⁸-A²⁹-A³⁰-A³¹-A³²-A³³-A³⁴-A³⁵-A³⁶-A³⁷-A³⁸-R³,

(IV)

or a pharmaceutically acceptable salt thereof, wherein

30 A¹ is Ala, Ser, Dap, Thr, Aib or is deleted;

A² is Val or is deleted;

A³ is Ser, Aib, Thr or is deleted;

A⁴ is Glu, Asp or is deleted;

A⁵ is His, Ile, Acc, Val, Nle, Phe, Leu, p-X-Phe, β-Nal, Aib, Cha or is deleted;

A⁶ is Gln, a hydrophilic amino acid or is deleted;

A⁷ is Leu, Val, Cha, Nle, β-Nal, Trp, Pal, Acc, Phe, p-X-Phe, Aib, a lipophilic amino acid or is deleted;

5 A⁸ is Leu, Met, Acc, Cha, Aib, Nle, Phe, Ile, Val, β-Nal, p-X-Phe, a lipophilic amino acid or is deleted;

A⁹ is His, a hydrophilic amino acid or is deleted;

A¹⁰ is Asp, Asn, a hydrophilic amino acid or is deleted;

A¹¹ is Lys, Arg, Leu, Cha, Aib, p-X-Phe, Ile, Val, Nle, Acc, Phe, β-Nal, HN-CH((CH₂)_nNH-R⁴)-

10 C(O), a lipophilic D-amino acid, a hydrophilic amino acid or is deleted;

A¹² is Gly, Acc, Aib or is deleted;

A¹³ is Lys, Arg, HN-CH((CH₂)_nNH-R⁴)-C(O) or is deleted;

A¹⁴ is Ser, His or is deleted;

A¹⁵ is Ile, Acc, Cha, Leu, Phe, Nle, β-Nal, Trp, p-X-Phe, Val, Aib or is deleted;

15 A¹⁶ is Gln, Aib or is deleted;

A¹⁷ is Asp, Aib or is deleted;

A¹⁸ is Leu, Aib, Acc, Cha, Phe, Ile, Nle, β-Nal, Val, p-X-Phe or is deleted,

A¹⁹ is Arg, Lys, Aib, HN-CH((CH₂)_nNH-R⁴)-C(O) or is deleted;

A²⁰ is Arg, Lys, HN-CH((CH₂)_nNH-R⁴)-C(O) or is deleted;

20 A²¹ is Arg, Lys, HN-CH((CH₂)_nNH-R⁴)-C(O) or is deleted;

A²² is Phe, Glu, Aib, Acc, p-X-Phe, β-Nal, Val, Leu, Ile, Nle or Cha;

A²³ is Phe, Leu, Lys, Acc, Cha, β-Nal, Aib, Nle, Ile, p-X-Phe, Val or Trp;

A²⁴ is Leu, Lys, Acc, Nle, Ile, Val, Phe, β-Nal, Aib, p-X-Phe, Arg or Cha;

A²⁵ is His, Lys, Aib, Acc, Arg or Glu;

25 A²⁶ is His, Aib, Acc, Arg or Lys;

A²⁷ is Leu, Lys, Acc, Arg, Ile, Val, Phe, Aib, Nle, β-Nal, p-X-Phe or Cha;

A²⁸ is Ile, Leu, Lys, Acc, Cha, Val, Phe, p-X-Phe, Nle, β-Nal, Aib or is deleted;

A²⁹ is Ala, Glu, Acc, Aib or is deleted;

A³⁰ is Glu, Leu, Nle, Cha, Aib, Acc, Lys, Arg or is deleted;

30 A³¹ is Ile, Leu, Cha, Lys, Acc, Phe, Val, Nle, β-Nal, Arg or is deleted,

A³² is His or is deleted;

A³³ is Thr, Ser or is deleted;

A³⁴ is Ala, Phe, Tyr, Cha, Val, Ile, Leu, Nle, β-Nal, Aib, Acc or is deleted;

A³⁵ is Glu, Asp or is deleted;

A³⁶ is Ile, Acc, Cha, Leu, Phe, Nle, β-Nal, Trp, p-X-Phe, Val, Aib or is deleted;

A³⁷ is Arg, Lys, HN-CH((CH₂)_nNH-R⁴)-C(O) or is deleted;

5 A³⁸ is Ala, Phe, Tyr, Cha, Val, Ile, Leu, Nle, β-Nal, Aib, Acc or is deleted;

R¹ and R² are each independently selected from the group consisting of H, (C₁₋₃₀)alkyl, (C₂₋₃₀)alkenyl, phenyl-(C₁₋₃₀)alkyl, naphthyl(C₁₋₃₀)alkyl, hydroxy(C₁₋₃₀)alkyl, hydroxy(C₂₋₃₀)alkenyl, hydroxy-phenyl(C₁₋₃₀)alkyl or hydroxy-naphthyl(C₁₋₃₀)alkyl.

10 or one of R¹ or R² is COE¹ where E¹ is (C₁₋₃₀)alkyl, (C₂₋₃₀)alkenyl, phenyl(C₁₋₃₀)alkyl, naphthyl(C₁₋₃₀)alkyl, hydroxy(C₁₋₃₀)alkyl, hydroxy(C₂₋₃₀)alkenyl, hydroxy-phenyl(C₁₋₃₀)alkyl or hydroxy-naphthyl(C₁₋₃₀)alkyl;

R³ is OH, NH₂, (C₁₋₃₀)alkoxy or NH-Y-CH₂-Z, where Y is a (C₁₋₃₀) hydrocarbon moiety and Z is CO₂H or CONH₂;

n for each occurrence is independently an integer from 1 to 5; and

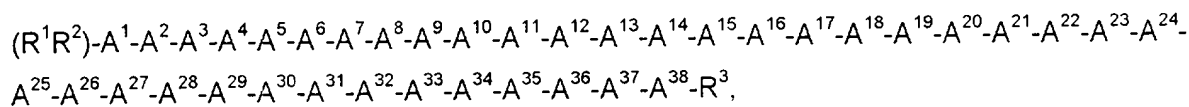
15 R⁴ for each occurrence is independently (C_{1-C30})alkyl, (C_{1-C30})acyl or -C((NH)(NH₂));
provided that the compound is not PTHrP(1-34)R³, PTHrP(1-35)R³, PTHrP(1-36)R³,
PTHrP(1-37)R³ or PTHrP(1-38)R³,
and further provided that the compound is not [Ile⁵, Trp²³]PTHrP(1-36) or [Trp²³]PTHrP(1-36).

20 In another aspect, this invention provides a method of selectively binding the PTH2 receptor which comprises administering to a patient in need thereof an effective amount of a PTH analogue or a truncated PTH analogue or a pharmaceutically acceptable salt thereof that selectively binds to a PTH2 receptor.

25 In another aspect, this invention provides a method of selectively eliciting an agonist response from the PTH2 receptor which comprises administering to a patient in need thereof an effective amount of a PTH analogue or a truncated PTH analogue or a pharmaceutically acceptable salt thereof which is a selective PTH2 receptor agonist.

30 In another aspect, this invention provides a method of selectively eliciting an antagonist response from the PTH2 receptor which comprises administering to a patient in need thereof an effective amount of a PTH analogue or a truncated PTH analogue or a pharmaceutically acceptable salt thereof which is a selective PTH2 receptor antagonist.

In yet another aspect, this invention provides a compound of the formula (III),



(III)

or a pharmaceutically-acceptable salt thereof wherein

- 5 A^1 is Ser, Ala, Dap, Thr, Aib or is deleted;
 A^2 is Val, Leu, Ile, Phe, Nle, β -Nal, Aib, p-X-Phe, Acc, Cha, Met or is deleted;
 A^3 is Ser, Thr, Aib or is deleted;
 A^4 is Glu, Asp or is deleted;
 A^5 is Leu, Val, Nle, Ile, Cha, β -Nal, Trp, Pal, Acc, Phe, p-X-Phe or is deleted;
- 10 A^6 is Gln, a hydrophilic amino acid or is deleted;
 A^7 is Leu, Val, Nle, Ile, Cha, β -Nal, Trp, Pal, Acc, Phe, p-X-Phe, a lipophilic amino acid, or is deleted;
 A^8 is Met, Nva, Leu, Val, Ile, Cha, Acc, Nle, p-X-Phe, Phe, β -Nal, Bpa, a lipophilic amino acid or is deleted;
- 15 A^9 is His, a hydrophilic amino acid or is deleted;
 A^{10} is Asn, a hydrophilic amino acid or is deleted;
 A^{11} is Leu, Val, Nle, Ile, Cha, β -Nal, Trp, Pal, Acc, Phe, p-X-Phe, a hydrophilic amino acid or is deleted;
 A^{12} is Gly, Acc, Aib, or is deleted;
- 20 A^{13} is Lys, Arg or $HN-CH((CH_2)_nNH-R^4)-C(O)$;
 A^{14} is His or is deleted;
 A^{15} is Leu, Val, Nle, Ile, Cha, β -Nal, Trp, Pal, Acc, Phe, p-X-Phe or is deleted;
 A^{16} is Ser, Asn, Ala, Aib or is deleted;
 A^{17} is Ser, Thr, Aib or is deleted;
- 25 A^{18} is Met, Nva, Leu, Val, Ile, Nle, p-X-Phe, Phe, β -Nal, Acc, Cha, Aib or is deleted;
 A^{19} is Glu, Aib or is deleted;
 A^{20} is Arg, Lys, $HN-CH((CH_2)_nNH-R^4)-C(O)$ or is deleted;
 A^{21} is Val, Leu, Ile, Phe, Nle, β -Nal, Aib, p-X-Phe, Acc, Cha, Met or is deleted;
 A^{22} is Acc, Aib, Glu or is deleted;
- 30 A^{23} is Trp, Acc, Phe, p-X-Phe, Aib, β -Nal or Cha;
 A^{24} is Leu, Acc, Ile, Val, Phe, β -Nal, Nle, Aib, p-X-Phe or Cha;
 A^{25} is Arg, Lys or $HN-CH((CH_2)_nNH-R^4)-C(O)$;

A²⁶ is Arg, Lys or HN-CH((CH₂)_nNH-R⁴)-C(O);

A²⁷ is Lys, Aib, Leu, hArg, Gln, Acc, Arg, Cha, Nle, Ile, Val, Phe, β-Nal, or p-X-Phe, where the Lys is optionally substituted on the ε-amino group by an acyl group;

A²⁸ is Leu, Acc, Cha, Ile, Val, Phe, Nle, β-Nal, Aib or p-X-Phe;

5 A²⁹ is Gln, Acc or Aib;

A³⁰ is Asp, Lys, Arg or is deleted;

A³¹ is Val, Leu, Nle, Acc, Cha, Phe, Ile, β-Nal Aib, p-X-Phe or is deleted;

A³² is His or is deleted;

A³³ is Asn or is deleted;

10 A³⁴ is Phe, Tyr, Amp, Aib, β-Nal, Cha, Nle, Leu, Ile, Acc, p-X-Phe or is deleted;

A³⁵ is Val, Leu, Nle, Acc, Cha, Phe, Ile, β-Nal Aib, p-X-Phe or is deleted;

A³⁶ is Ala, Val, Aib, Acc, Nva, Abu or is deleted;

A³⁷ is Leu, Val, Nle, Ile, Cha, β-Nal, Trp, Pal, Acc, Phe, p-X-Phe, a lipophilic amino acid, or is deleted;

15 A³⁸ is Gly, Acc, Aib, or is deleted;

where X for each occurrence is independently selected from the group consisting of OH, a halo and CH₃;

R¹ and R² are each independently selected from the group consisting of H, (C₁₋₃₀)alkyl, (C₂₋₃₀)alkenyl, phenyl-(C₁₋₃₀)alkyl, naphthyl(C₁₋₃₀)alkyl, hydroxy(C₁₋₃₀)alkyl, hydroxy(C₂₋₃₀)alkenyl, hydroxy-phenyl(C₁₋₃₀)alkyl or hydroxy-naphthyl(C₁₋₃₀)alkyl;

20 or one of R¹ or R² is COE¹ where E¹ is (C₁₋₃₀)alkyl, (C₂₋₃₀)alkenyl, phenyl(C₁₋₃₀)alkyl, naphthyl(C₁₋₃₀)alkyl, hydroxy(C₁₋₃₀)alkyl, hydroxy(C₂₋₃₀)alkenyl, hydroxy-phenyl(C₁₋₃₀)alkyl or hydroxy-naphthyl(C₁₋₃₀)alkyl;

R³ is OH, NH₂, (C₁₋₃₀)alkoxy or NH-Y-CH₂-Z, where Y is a (C₁₋₃₀) hydrocarbon moiety and Z is CO₂H or CONH₂;

25 n for each occurrence is independently an integer from 1 to 5; and

R⁴ for each occurrence is independently (C_{1-C30})alkyl, (C_{1-C30})acyl or -C((NH)(NH₂));

provided that when A⁸ is not a lipophilic D-amino acid or is not deleted then at least one of A⁶, A⁷, A⁹, A¹⁰, A¹¹ and A¹² is a D-amino acid or at least one of A⁶, A⁷, A⁹, A¹⁰, A¹¹, A¹², A¹³,

30 A¹⁴, A¹⁵, A¹⁶, A¹⁷, A¹⁸, A¹⁹, A²⁰, A²¹ and A²² is deleted;

and further provided that when the compound contains a D-amino acid then A³⁶ is deleted.

A preferred group of compounds of formula (III) are the compounds listed as Examples 1-73, shown hereinbelow. Of the compounds listed as Examples 1-73, the following compounds are preferred: [Cha^{7,11}, des-Met⁸, Nle¹⁸, Tyr³⁴]hPTH-(1-34)NH₂, [Cha^{7,11}, D-Nle⁸, des-Met¹⁸, Tyr³⁴]hPTH-(1-34)NH₂, [Cha^{7,11}, D-Nle⁸, Nle¹⁸, Tyr³⁴]hPTH-(1-34)NH₂, [D-Nle⁸, Nle¹⁸, Tyr³⁴]hPTH(1-34)NH₂ and [D-Bpa⁸, Tyr³⁴]hPTH(1-34)NH₂.

In yet another aspect, this invention provides a compound of formula (V),

$$(R^1R^2)-A^1-A^2-A^3-A^4-A^5-A^6-A^7-A^8-A^9-A^{10}-A^{11}-A^{12}-A^{13}-A^{14}-A^{15}-A^{16}-A^{17}-A^{18}-A^{19}-A^{20}-A^{21}-A^{22}-A^{23}-A^{24}-A^{25}-A^{26}-A^{27}-A^{28}-A^{29}-A^{30}-A^{31}-A^{32}-A^{33}-A^{34}-A^{35}-A^{36}-A^{37}-A^{38}-R^3,$$

(V)

or a pharmaceutically acceptable salt thereof, wherein

A¹ is Ala, Ser, Dap, Thr, Aib or is deleted;

A² is Val or is deleted;

A³ is Ser, Aib, Thr or is deleted;

A⁴ is Glu, Asp or is deleted;

A⁵ is His, Ile, Acc, Val, Nle, Phe, Leu, p-X-Phe, β-Nal, Aib, Cha or is deleted;

A⁶ is Gln, a hydrophilic amino acid or is deleted;

A⁷ is Leu, Val, Cha, Nle, β-Nal, Trp, Pal, Acc, Phe, p-X-Phe, Aib, a lipophilic amino acid or is deleted;

A⁸ is Leu, Met, Acc, Cha, Aib, Nle, Phe, Ile, Val, β-Nal, p-X-Phe, a lipophilic amino acid or is deleted;

A⁹ is His, a hydrophilic amino acid or is deleted;

A¹⁰ is Asp, Asn, a hydrophilic amino acid or is deleted;

A¹¹ is Lys, Arg, Leu, Cha, Aib, p-X-Phe, Ile, Val, Nle, Acc, Phe, β-Nal, HN-CH((CH₂)_nNH-R⁴)-C(O), a lipophilic D-amino acid, a hydrophilic amino acid or is deleted;

A¹² is Gly, Acc, Aib or is deleted;

A¹³ is Lys, Arg, HN-CH((CH₂)_nNH-R⁴)-C(O) or is deleted;

A¹⁴ is Ser, His or is deleted;

A¹⁵ is Ile, Acc, Cha, Leu, Phe, Nle, β-Nal, Trp, p-X-Phe, Val, Aib or is deleted;

A¹⁶ is Gln, Aib or is deleted;

A¹⁷ is Asp, Aib or is deleted;

A¹⁸ is Leu, Aib, Acc, Cha, Phe, Ile, Nle, β-Nal, Val, p-X-Phe or is deleted.

A¹⁹ is Arg, Lys, Aib, HN-CH((CH₂)_nNH-R⁴)-C(O) or is deleted;

- A²⁰ is Arg, Lys, HN-CH((CH₂)_nNH-R⁴)-C(O) or is deleted;
A²¹ is Arg, Lys, HN-CH((CH₂)_nNH-R⁴)-C(O) or is deleted;
A²² is Phe, Glu, Aib, Acc, p-X-Phe, β-Nal, Val, Leu, Ile, Nle or Cha;
A²³ is Phe, Leu, Lys, Acc, Cha, β-Nal, Aib, Nle, Ile, p-X-Phe, Val or Trp;
5 A²⁴ is Leu, Lys, Acc, Nle, Ile, Val, Phe, β-Nal, Aib, p-X-Phe, Arg or Cha;
A²⁵ is His, Lys, Aib, Acc, Arg or Glu;
A²⁶ is His, Aib, Acc, Arg or Lys;
A²⁷ is Leu, Lys, Acc, Arg, Ile, Val, Phe, Aib, Nle, β-Nal, p-X-Phe or Cha;
A²⁸ is Ile, Leu, Lys, Acc, Cha, Val, Phe, p-X-Phe, Nle, β-Nal, Aib or is deleted;
10 A²⁹ is Ala, Glu, Acc, Aib or is deleted;
A³⁰ is Glu, Leu, Nle, Cha, Aib, Acc, Lys, Arg or is deleted;
A³¹ is Ile, Leu, Cha, Lys, Acc, Phe, Val, Nle, β-Nal, Arg or is deleted;
A³² is His or is deleted;
A³³ is Thr, Ser or is deleted;
15 A³⁴ is Ala, Phe, Tyr, Cha, Val, Ile, Leu, Nle, β-Nal, Aib, Acc or is deleted;
A³⁵ is Glu, Asp or is deleted;
A³⁶ is Ile, Acc, Cha, Leu, Phe, Nle, β-Nal, Trp, p-X-Phe, Val, Aib or is deleted;
A³⁷ is Arg, Lys, HN-CH((CH₂)_nNH-R⁴)-C(O) or is deleted;
A³⁸ is Ala, Phe, Tyr, Cha, Val, Ile, Leu, Nle, β-Nal, Aib, Acc or is deleted;
20 R¹ and R² are each independently selected from the group consisting of H, (C₁₋₃₀)alkyl, (C₂₋₃₀)alkenyl, phenyl-(C₁₋₃₀)alkyl, naphthyl(C₁₋₃₀)alkyl, hydroxy(C₁₋₃₀)alkyl, hydroxy(C₂₋₃₀)alkenyl, hydroxy-phenyl(C₁₋₃₀)alkyl or hydroxy-naphthyl(C₁₋₃₀)alkyl, or one of R¹ or R² is COE¹ where E¹ is (C₁₋₃₀)alkyl, (C₂₋₃₀)alkenyl, phenyl(C₁₋₃₀)alkyl, naphthyl(C₁₋₃₀)alkyl, hydroxy(C₁₋₃₀)alkyl, hydroxy(C₂₋₃₀)alkenyl, hydroxy-phenyl(C₁₋₃₀)alkyl or hydroxy-naphthyl(C₁₋₃₀)alkyl;
25 R³ is OH, NH₂, (C₁₋₃₀)alkoxy or NH-Y-CH₂-Z, where Y is a (C₁₋₃₀) hydrocarbon moiety and Z is CO₂H or CONH₂;
n for each occurrence is independently an integer from 1 to 5; and
R⁴ for each occurrence is independently (C₁₋₃₀)alkyl, (C₁₋₃₀)acyl or -C((NH)(NH₂));
30 provided that when A⁸ is not a lipophilic D-amino acid or is not deleted then at least one of A⁶, A⁷, A⁹, A¹⁰, A¹¹ and A¹² is a D-amino acid or at least one of A⁶, A⁷, A⁹, A¹⁰, A¹¹, A¹², A¹³, A¹⁴, A¹⁵, A¹⁶, A¹⁷, A¹⁸, A¹⁹, A²⁰, A²¹ and A²² is deleted.

A preferred group of compounds of formula (V) are the compounds listed as Examples 74-86, shown hereinbelow.

In a further aspect, this invention provides a method of selectively binding the PTH2 receptor which comprises administering to a patient in need thereof an analogue of formula (I), (II) or (III) or a pharmaceutically acceptable salt thereof.

In another aspect, this invention provides a method of selectively binding the PTH2 receptor which comprises administering to a patient in need thereof a compound of formula (III) or (V) or a pharmaceutically acceptable salt thereof. Preferred of the foregoing method is where the compound is selected from Examples 1-73 or Examples 74-86.

In another aspect, this invention is directed to a pharmaceutical composition comprising an analogue of formula (I), (II) or (III) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

In still another aspect, this invention is directed to a pharmaceutical composition comprising a compound of formula (III) or (V) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier. Preferred is a pharmaceutical composition comprising a compound selected from Examples 1-73 or Examples 74-86.

In still another aspect, this invention is directed to a method of treating a medical disorder that results from altered or excessive action of the PTH2 receptor, which comprises administering to a patient in need thereof an effective amount of a PTH analogue or a truncated PTH analogue or a pharmaceutically acceptable salt thereof that selectively binds to the PTH2 receptor, sufficient to inhibit the activation of the PTH2 receptor of said patient. A preferred method of the immediately foregoing method is where said medical disorder is abnormal CNS functions, abnormal pancreatic functions, divergence from normal mineral metabolism and homeostasis, male infertility, abnormal blood pressure or a hypothalamic disease. Preferred of each of the immediately foregoing methods is where the analogue is a PTH2 agonist or a PTH2 antagonist.

In another aspect, this invention provides a method of treating a medical disorder that results from altered or excessive action of the PTH2 receptor, which comprises administering to a patient in need thereof an effective amount of an analogue of formula (I), (II) or (III), sufficient to inhibit the activation of the PTH2 receptor of said patient. A preferred method of the immediately foregoing method is where said medical disorder is abnormal CNS functions, abnormal pancreatic functions, divergence from normal mineral metabolism and homeostasis, male infertility, abnormal blood pressure or a hypothalamic disease.

In another aspect, this invention is directed to a method of treating a medical disorder that results from altered or excessive action of the PTH2 receptor, which comprises administering to a patient in need thereof an effective amount of a compound of formula (III) or (V), sufficient to inhibit the activation of the PTH2 receptor of said patient. A preferred method of the immediately foregoing method is where said medical disorder is abnormal CNS functions, abnormal pancreatic functions, divergence from normal mineral metabolism and homeostasis, male infertility, abnormal blood pressure or a hypothalamic disease. Preferred of each of the foregoing methods is where the compound is selected from Examples 1-73 or Examples 74-86.

Detailed Description

With the exception of the N-terminal amino acid, all abbreviations (e.g. Ala or A₁) of amino acids in this disclosure stand for the structure of -NH-CH(R)-CO-, wherein R is the side chain of an amino acid (e.g., CH₃ for Ala). For the N-terminal amino acid, the abbreviation stands for the structure of (R¹R²)-N-CH(R)-CO-, wherein R is a side chain of an amino acid and R¹ and R² are as defined above. Bpa is p-benzoylphenylalanine. β-Nal, Nle, Dap, Cha, Nva, Amp, Pal, and Aib are the abbreviations of the following α-amino acids: β-(2-naphthyl)alanine, norleucine, α,β-diaminopropionic acid, cyclohexylalanine, norvaline, 4-amino-phenylalanine, β-(3-pyridinyl)alanine and α-aminoisobutyric acid, respectively. What is meant by Acc is an amino acid selected from the group of 1-amino-1-cyclopropanecarboxylic acid; 1-amino-1-cyclobutanecarboxylic acid; 1-amino-1-cyclopentanecarboxylic acid; 1-amino-1-cyclohexanecarboxylic acid; 1-amino-1-cycloheptanecarboxylic acid; 1-amino-1-cyclooctanecarboxylic acid; and 1-amino-1-cyclononanecarboxylic acid. In the above formula, hydroxyalkyl, hydroxyphenylalkyl, and hydroxynaphthylalkyl may contain 1-4 hydroxy substituents. COE₁ stands for -C=O·E¹. Examples of -C=O·E¹ include, but are not limited to, acetyl and phenylpropionyl. What is meant by "(C₁₋₁₂) hydrocarbon moiety" is an alkyl group, an alkenyl group or an alkynyl group.

What is meant by a "hydrophilic amino acid" is an amino acid having at least one hydrophilic functional group in addition to those required for peptide bond formation, such as: Arg, Asp, Asn, Glu, Gln, Gly, His, Lys, Orn (ornithine), Ser, Thr, β-Ala, Ala, Aad (α-amino adipic acid), β-Aad (β-amino adipic acid), Apm (α-aminopimolic acid), Cit (citrulline), Gla (γ-carboxy-glutamic acid), hArg (homo-Arg), hCit (homo-Cit), hSer (homo-Ser), Dbal (α,γ-

diamino-butyric acid), Dpa (α,β -diaminopropionic acid), Amp (p-amino-phenylalanine), Pal, and their homologues.

What is meant by a "lipophilic amino acid" is an uncharged, aliphatic or aromatic amino acid, such as: Val, Leu, Ile, Pro, Cys, Phe, Met, Trp, Tyr, Cha, β -Nal, Aib, Acc, Ala, Abu (α -aminobutyric acid), Nle, Nva (norvaline), Bpa (p-benzoyl-phenylalanine), hPhe (homo-Phe), hPro (homo-Pro), 1-Nal(β -(1-naphthyl)alanine), 2-Nal (β (2-naphthyl)alanine), Oic (octahydroindode-2-carboxylic acid), Tic (1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid), Pen (penicillamine), Phg (phenylglycine), Tie (t-leucine), p-X-Phe (X= Br, F, I, Cl, CH, phenyl, CN, NO₂), Tal (β -(2-thienyl)-alanine), and their homologues.

Alanine, β -alanine and sarcosine (Sar) may be considered either a hydrophilic or a lipophilic amino acid.

"Physiologically active truncated homologue or analogue of PTH" refers to a polypeptide having a sequence comprising less than the full complement of amino acids found in PTH.

The full names for other abbreviations used herein are as follows: Boc for t-butyloxycarbonyl, HF for hydrogen fluoride, Fm for formyl, Xan for xanthyl, Bzl for benzyl, Tos for tosyl, DNP for 2,4-dinitrophenyl, DMF for dimethylformamide, DCM for dichloromethane, HBTU for 2-(1H-Benzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate, DIEA for diisopropylethylamine, HOAc for acetic acid, TFA for trifluoroacetic acid, 2CIZ for 2-chlorobenzyloxycarbonyl and OcHex for O-cyclohexyl.

A peptide of this invention is also denoted herein by another format, e.g., [D-Nle⁸]hPTH(1-34)NH₂, with the substituted amino acids from the natural sequence placed between the set of brackets (e.g., D-Nle⁸ for Met⁸ in hPTH). The abbreviation hPTH stands for human PTH, and hPTHrP for human PTHrP. The numbers between the parentheses refer to the number of amino acids present in the peptide (e.g., hPTH(1-34) is amino acids 1 through 34 of the peptide sequence for human PTH). The sequences for hPTH(1-34) and hPTHrP(1-34) are listed in Nissenson, et al., Receptor, 3:193 (1993). The designation "NH₂" in PTH(1-34)NH₂ indicates that the C-terminus of the peptide is amidated. PTH(1-34) means that the C-terminus is the free acid.

The peptides of this invention can be prepared by standard solid phase peptide synthesis. See, e.g., Stewart, J.M., et al., Solid Phase Synthesis (Pierce Chemical Co., 2d ed. 1984). The substituents R¹ and R² of the above generic formula may be attached to the free amine of the N-terminal amino acid by standard methods known in the art. For

example, alkyl groups, e.g., (C₁₋₁₂)alkyl, may be attached using reductive alkylation. Hydroxyalkyl groups, e.g., (C₁₋₁₂)hydroxyalkyl, may also be attached using reductive alkylation wherein the free hydroxy group is protected with a t-butyl ester. Acyl groups, e.g., COE¹, may be attached by coupling the free acid, e.g., E¹COOH, to the free amine of the N-terminal amino acid by mixing the completed resin with 3 molar equivalents of both the free acid and diisopropylcarbodiimide in methylene chloride for one hour. If the free acid contains a free hydroxy group, e.g., p-hydroxyphenylpropionic acid, then the coupling should be performed with an additional 3 molar equivalents of HOBT.

When R³ is NH-Y-CH₂-CONH₂ (Z=CONH₂), the synthesis of the peptide starts with BocHN-Y-CH₂-COOH which is coupled to the resin. If R³ is NH-Y-CH₂-COOH (Z=COOH) the synthesis of the peptide starts with Boc-HN-Y-CH₂-COOH which is coupled to PAM resin. When R³ is OH the first amino acid is coupled to PAM resin.

The compounds of this invention can be tested for binding to the human PTH₂ (hPTH₂) receptor for the ability to stimulate adenylyl cyclase and/or intracellular calcium transients by the assay described below.

Materials and Methods: Tissue culture media and sera were purchased from Life Technologies (Grand Island, NY), and all tissue culture plastics were obtained from Corning (Corning, NY). Adenosine and 3-isobutyl-1-methyl xanthine (IBMX) were purchased from Research Biochemicals (Natick, MA). Fura-2 acetoxymethyl ester (fura-2/AM) was obtained from Molecular Probes (Eugene, OR), and hPTHrP was purchased from Bachem (Torrance, CA). [³H]-Adenine was purchased from New England Nuclear (Boston, MA). Na¹²⁵I was obtained from Amersham Corp. (Arlington Heights, IL). All other analytical grade reagents were purchased from Sigma (St. Louis, MO).

Cell Culture: Human osteosarcoma Saos-2/B-10 cells (American Type Culture Collection, Rockville, MD; ATCC #HTB 85) are maintained in RPMI 1640 medium (Sigma, St. Louis, MO) supplemented with 10% fetal bovine serum (FBS) and 2 mM glutamine at 37°C in a humidified atmosphere of 5% CO₂ in air. The medium is changed every three or four days, and the cells are subcultured every week by trypsinization. Stably transfected HEK-293/BP-16 cells (Beth Israel Deaconess Medical Center-Division of Bone and Mineral Metabolism, Boston, MA), which express the hPTH₂ receptor (160,000 receptors/cell) and stably transfected HEK-293/C-21 cells (Beth Israel Deaconess Medical Center-Division of Bone and Mineral Metabolism, Boston, MA), which express the hPTH/PTHrP receptor, are maintained in DMEM supplemented with 10% FBS at 37°C in a humidified atmosphere of

95% air/5% CO₂. The medium is changed every 2 days before confluency and every day after confluency. The cells are sub-cultured 1:10 once a week.

Receptor binding assay: Ligand binding is performed using Saos-2/B-10, HEK/C-21 cells or HEK/BP-16 cells using HPLC-purified [¹²⁵I][Nle^{8,18}, Tyr³⁴]bPTH-(1-34)NH₂ (¹²⁵I-PTH) as radioligand. Saos-2 cells are maintained for four days until they reach confluence. The medium is replaced with 5% FBS in RPMI 1640 medium and incubated for about 2 hrs at room temperature with 10 x 10⁴ cpm mono-¹²⁵I-[Nle^{8,18}, Tyr³⁴(3-¹²⁵I)]bPTH(1-34)NH₂ in the presence of competing peptides of the invention at various concentrations between 10⁻¹¹M to 10⁻⁴ M. The cells are washed four times with ice-cold PBS and lysed with 0.1 M NaOH, and the radioactivity associated with the cells is counted in a scintillation counter. Synthesis of mono-¹²⁵I-[Nle^{8,18}, Tyr³⁴(3-¹²⁵I)]bPTH(1-34)NH₂ is carried out as described in Goldman, M.E., et al., Endocrinol. 123 1468 (1988).

The binding assay is conducted with various peptides of the invention, and the K_d value (half maximal inhibition of binding of mono-¹²⁵I-[Nle^{8,18}, Tyr³⁴(3-¹²⁵I)]bPTH(1-34)NH₂) for each peptide is calculated

Adenylyl cyclase assay: Adenylyl cyclase assay is performed in Saos-2/B-10 cells, HEK/C21 cells, and HEK/BP-16 cells. The ability of the peptides of the invention to induce a biological response in Saos-2/B-10 cells is measured. More specifically, any stimulation of the adenylyl cyclase is determined by measuring the level of synthesis of cAMP (adenosine 3',5'-monophosphate) as described previously in Rodan, et al., J. Clin. Invest. 72: 1511 (1983) and Goldman, et al., Endocrinol., 123:1468 (1988). Confluent Saos-2/B-10 cells in 24 well plates at 4x10⁴ cells/well in RPMI1640 medium containing 10% FBS. Cells are washed twice with Ca²⁺ and Mg²⁺ free Hanks' balanced salt solution and incubated with 0.5 µCi [³H]adenine (26.9 Ci/mmol, New England Nuclear, Boston, MA) in fresh medium at about 37°C for about 2 hrs, and washed twice with Hank's balanced salt solution (Gibco, Gaithersburg, MD). The cells are treated with 1 mM IBMX [isobutylmethyl-xanthine, Sigma, St. Louis, MO] in fresh medium for 15 min, and a peptide to be tested is added to the medium to incubate for about 5 min. The reaction is stopped by the addition of 1.2 M trichloroacetic acid (TCA) (Sigma, St. Louis, MO) followed by sample neutralization with 4 N KOH. cAMP is isolated by the two-column chromatographic method (Salmon, et al., 1974, Anal. Biochem. 58, 541). The radioactivity is counted in a scintillation counter (Liquid Scintillation Counter 2200CA, PACKARD, Downers Grove, IL).

Measurements of $[Ca^{2+}]_i$: Measurements of intracellular Ca^{2+} ($[Ca^{2+}]_i$) are performed in Saos-2/B-10 cells, HEK/C-21 cells and HEK/BP-16 cells. For measurement of $[Ca^{2+}]_i$, cells are harvested from 150-cm² flasks using HEPES-buffered balanced salt solution containing 0.02% (vol/vol) EDTA. The cell suspension is washed three times with Hanks' Balanced Salt Solution (1 mM $CaCl_2$, 118 mM NaCl, 4.6 mM KCl, 10 mM d-glucose, and 20 mM HEPES, pH 7.4), and cells are loaded with fura-2/AM (1 μ M) for about 40 min at about 37°C. The cell suspension is washed three times with Hanks' Balanced Salt Solution, and fluorescence is measured in a SPEX AR-CM system spectrofluorimeter (SPEX Industries, Edison, NJ). Dual wavelength measurements are performed (excitation wavelengths, 340 and 380 nm; emission wavelength, 505 nm).

$[Ca^{2+}]_i$ is calculated from fura-2 ratios (R) by the equation: $[Ca^{2+}]_i = K (R - R_{min}) / (R_{max} - R)$, where R_{min} and R_{max} are the ratios (e.g. 340 nm/380 nm) for the minimal or maximal calcium concentration, respectively. K is the product $K_d(F_0/F_s)$, where K_d is the effective dissociation constant (224 nM), F_0 is the intensity of the 380-nm excitation signal in the absence of calcium, and F_s is the intensity of the 380-nm excitation signal at saturating calcium concentrations. Maximum fluorescence intensity is obtained by permeabilizing the cells with 50 μ M digitonin in the presence of 1 mM $CaCl_2$, and minimal fluorescence intensity is obtained by chelating calcium with 16.6 mM EGTA [pH adjusted to 8.3 with 1M Tris-(hydroxymethyl)aminomethane base]. Addition of vehicle alone (0.1% BSA in PBS) did not change the level of $[Ca^{2+}]_i$.

The peptides of this invention can be provided in the form of pharmaceutically acceptable salts. Examples of such salts include, but are not limited to, those formed with organic acids (e.g., acetic, lactic, maleic, citric, malic, ascorbic, succinic, benzoic, methanesulfonic, toluenesulfonic or pamoic acid), inorganic acids (e.g., hydrochloric acid, sulfuric acid, or phosphoric acid), and polymeric acids (e.g., tannic acid, carboxymethyl cellulose, polylactic, polyglycolic, or copolymers of polylactic-glycolic acids).

A therapeutically effective amount of a peptide of this invention and a pharmaceutically acceptable carrier substance (e.g., magnesium carbonate, lactose, or a phospholipid with which the therapeutic compound can form a micelle) together form a therapeutic composition (e.g., a pill, tablet, capsule, or liquid) for administration (e.g., orally, intravenously, transdermally, pulmonarily, vaginally, subcutaneously, nasally, iontophoretically, or by intratracheally) to a subject. The pill, tablet or capsule that is to be administered orally can be coated with a substance for protecting the active composition

from the gastric acid or intestinal enzymes in the stomach for a period of time sufficient to allow it to pass undigested into the small intestine. The therapeutic composition can also be in the form of a biodegradable or nonbiodegradable sustained release formulation for subcutaneous or intramuscular administration. See, e.g., U.S. Patents 3,773,919 and 4,767,628 and PCT Application No. WO 94/15587. Continuous administration can also be achieved using an implantable or external pump (e.g., INFUSAID™ pump). The administration can also be conducted intermittently, e.g., single daily injection, or continuously at a low dose, e.g., sustained release formulation.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, the elixirs containing inert diluents commonly used in the art, such as water. Besides such inert diluents, compositions can also include adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring and perfuming agents.

Preparations according to this invention for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, or emulsions. Examples of non-aqueous solvents or vehicles are propylene glycol, polyethylene glycol, vegetable oils, such as olive oil and corn oil, gelatin, and injectable organic esters such as ethyl oleate. Such dosage forms may also contain adjuvants such as preserving, wetting, emulsifying, and dispersing agents. They may be sterilized by, for example, filtration through a bacteria-retaining filter, by incorporating sterilizing agents into the compositions, by irradiating the compositions, or by heating the compositions. They can also be manufactured in the form of sterile solid compositions which can be dissolved in sterile water, or some other sterile injectable medium immediately before use.

Compositions for rectal or vaginal administration are preferably suppositories which may contain, in addition to the active substance, excipients such as coca butter or a suppository wax.

Compositions for nasal or sublingual administration are also prepared with standard excipients well known in the art.

Further, a compound of this invention can be administered in a sustained release composition such as those described in the following patents. U.S. Patent No. 5,672,659 teaches sustained release compositions comprising a bioactive agent and a polyester. U.S. Patent No. 5,595,760 teaches sustained release compositions comprising a bioactive agent in a gelable form. U.S. Application No. 08/929,363 filed September 9, 1997, teaches

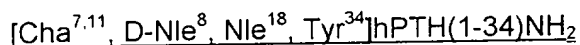
polymeric sustained release compositions comprising a bioactive agent and chitosan. U.S. Application No. 08/740,778 filed November 1, 1996, teaches sustained release compositions comprising a bioactive agent and cyclodextrin. U.S. Application No. 09/015,394 filed January 29, 1998, teaches absorbable sustained release compositions of a
5 bioactive agent. The teachings of the foregoing patents and applications are incorporated herein by reference.

The dosage of active ingredient in the compositions of this invention may be varied; however, it is necessary that the amount of the active ingredient be such that a suitable dosage form is obtained. The selected dosage depends upon the desired therapeutic
10 effect, on the route of administration, and on the duration of the treatment. Generally, dosage levels of between 0.0001 to 10 mg/kg of body weight daily are administered.

A preferred dosage range is 0.001 to 0.5 mg/kg of body weight daily which can be administered as a single dose or divided into multiple doses.

The compounds of the instant invention are illustrated by the following examples, but
15 are not limited to the details thereof.

EXAMPLE 1



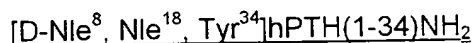
The peptide $[\text{Cha}^{7,11}, \text{D-Nle}^8, \text{Nle}^{18}, \text{Tyr}^{34}]\text{hPTH}(1-34)\text{NH}_2$ was synthesized on an Applied Biosystems (Foster City, CA) model 430A peptide synthesizer which was modified
20 to do accelerated Boc-chemistry solid phase peptide synthesis. See Schnoize, et al, Int J. Peptide Protein Res., 90:180 (1992). 4-Methylbenzhydrylamine (MBHA) resin (Peninsula, Belmont, CA) with the substitution of 0.93 mmol/g was used. The Boc amino acids (Bachem, CA, Torrance, CA; Nova Biochem., LaJolla, CA) were used with the following side chain protection: Boc-Asn(Xanthyl), Boc-Arg(Tos)-OH, Boc-Asp(OcHex)-OH, Boc-
25 Glu(OcHex)-OH, Boc-His(DNP)-OH, Boc-Cha-OH, Boc-D-Nle-OH, Boc-Nle-OH, Boc-Val-OH, Boc-Leu-OH, Boc-Gly-OH, Boc-Gln-OH, Boc-Ile-OH, Boc-Lys(2CIZ)-OH, Boc-Ser(Bzl)-OH; Boc-Trp(formyl)-OH and Boc-Tyr(Br-Z)-OH (where Z is benzyloxycarbonyl) The synthesis was carried out on a 0.14 mmol scale. The Boc groups were removed by treatment with 100% TFA for 2 x 1 min. Boc amino acids (2.5 mmol) were pre-activated
30 with HBTU (2.0 mmol) and DIEA (1.0 mL) in 4 mL of DMF and were coupled without prior neutralization of the peptide-resin TFA salt. Coupling times were about 5 min.

At the end of the assembly of the peptide chain, the resin was treated with a solution of 20% mercaptoethanol/10% DIEA in DMF for 2 x 30 min. to remove the DNP group on the

His side chain. The resin was washed with DMF. The N-terminal Boc group was then removed by treatment with 100% TFA for 2 x 2 min. The resin was washed with DMF and was treated with ethanolamine:H₂O:DMF/15:15:70 for 2 x 30 min. to remove the formyl protecting group on Trp residue. The partially-deprotected peptide-resin was washed with DMF and DCM and dried *in vacuo*. The final cleavage was done by stirring the peptide-resin in 10 mL of HF containing 1 mL of anisole and dithiothreitol (24 mg) at about 0°C for about 75 min. HF was removed by a flow of nitrogen. The residue was washed with ether (6 x 10 mL) and extracted with 4N HOAc (6 x 10 mL).

The peptide mixture in the aqueous extract was purified on a reverse-phase preparative high pressure liquid chromatography (HPLC) using a reverse phase VYDACTM C₁₈ column (Nest Group, Southborough, MA). The column was eluted with a linear gradient (10% to 45% of solution B in solution A over 130 min.) at a flow rate of 10 mL/min (Solution A = water containing 0.1% TFA; Solution B = acetonitrile containing 0.1% of TFA). Fractions were collected and checked on analytical HPLC. Those containing pure product were combined and lyophilized to dryness. 114 mg of a white solid was obtained. Purity was >98% based on analytical HPLC analysis. Electro-spray mass spectrometer analysis gave the molecular weight at 4176.4 (in agreement with the calculated molecular weight of 4176.9).

EXAMPLE 2



Boc-protected amino acids, N-hydroxybenzotriazole (HOBt), N,N'-dicyclohexylcarbodiimide (DCC) and *p*-methylbenzhydrylamine resin were purchased from Applied Biosystems (Foster City, CA). Boc-(3-Iodo)Tyrosine[O-(3-BrBz)] was purchased from Peninsula Laboratories (Belmont, CA). B&J brand dichloromethane. N-methylpyrrolidone (NMP) and acetonitrile were obtained from Baxter (McGraw Park, IL). All other reagents are commercially available, for example from Sigma (St. Louis, MO). The title peptide was synthesized by solid-phase Boc/HOBt/NMP chemistry on an automated Applied Biosystems 430A peptide synthesizer using software version 1.40. The following side-chain protected N- α -Boc-amino derivatives were used in the course of the automated solid-phase peptide synthesis: Arg(N^G-tosyl), Asp(O-cHex), Glu(O-Bzl), His(Nⁿ-Bom), Lys(N^ε-2-CI-Z), Ser(O-Bzl), Thr(O-Bzl), and Tyr(2-Br-Z). Synthesis started at a 0.5 mmol scale and was split into two halves after the incorporation of Glu²². The following residues were incorporated by double coupling cycles: Arg²⁵, Leu²⁴, Val²¹, Arg²⁰, Glu¹⁹, Leu¹⁵, His¹⁴,

Lys¹³, His⁹, Phe⁷, Gln⁶ and Ile⁵. The Nle in positions 18 and 8 was introduced in the form of pre-dissolved NMP solution and the Activator cycle was modified accordingly. Cleavage of the peptide from the ρ MBHA resin utilized liquid hydrogen fluoride and followed the "Low-High" procedure. The "Low-HF" step included mixing the suspension of the resin-bound peptide in a mixture (20 mL/g of resin-bound peptide) containing (% vol) 60% dimethylsulfide, 5% ρ -thiocresol, 5% ρ -cresol, 5% ethane dithiol, and 25% HF for about 2 hours at about 0°C. After removal of the volatile reagent under vacuum and washing the resin-bound peptide consecutively with petroleum-ether and ether it was returned to the reaction vessel for the "High-HF" step. The resin-bound peptide was resuspended in a mixture (20 mL/g of resin-bound peptide) containing (% vol) 5% butane dithiol, 5% ρ -cresol, and 90% HF for about 1 hour at about 0°C. After removing the reagents as previously described the crude peptide was dissolved in 50% (v/v) acetic acid and the solution was diluted with water and lyophilized. The peptide was purified by preparative reverse-phase high performance liquid chromatography (RP-HPLC) (PrepPak VYDAC® C18, 300Å cartridge, 15 μ m, 5.5x35 cm). The solvent system employed included a two solvent system: A: 0.1% (v/v) TFA in water and B: 0.1% (v/v) TFA in acetonitrile, generating the following linear gradient: 0-15% B in A in the first 10 min followed by 15-45% B in A in the next 120 min at a flow-rate of 70 mL/min and monitored at 220 nm. Fractions were analyzed on an analytical RP-HPLC system (VYDAC® (C18, 300Å, 5 μ m, 4.6x150cm) employing a linear gradient of 20-50% B in A for 30 min at a flow rate of 1 ml/min and monitored at 220 nm, the retention time is 18.24 minutes. The pure fractions were pooled and the acetonitrile removed under vacuum. The residual was lyophilized to yield a white powder. Purity and structure of the peptides were confirmed by analytical RP-HPLC, amino acid analysis, and Fast Atom Bombardment Mass Spectrometry, mass spec. = 4097.0.

EXAMPLES 3-5

Examples 3-4 were synthesized substantially according to the procedure of Example 1 using the appropriate, protected amino acids and Example 5 was synthesized substantially according to Example 2 using the appropriate, protected amino acids.

Example	Name	Mass Spec.
3	[Cha ^{7,11} , des-Met ⁸ , Nle ¹⁸ , Tyr ³⁴]hPTH(1-34)NH ₂	4063.5
4	[Cha ^{7,11} , D-Nle ⁸ , des-Met ¹⁸ , Tyr ³⁴]hPTH(1-34)NH ₂	4063.4
5	[D-Bpa ⁸ Tyr ³⁴]hPTH-(1-34)NH ₂	4320.7

EXAMPLES 6-86

Examples 6 to 86 can be synthesized substantially according to the procedure of Example 1 using the appropriate, protected amino acids.

- 5 Example 6: [D-Nle⁸, Nle¹⁸, Tyr³⁴]hPTH(1-34)NH₂
Example 7: [D-Nle⁸]hPTH(1-34)NH₂
Example 8: [D-Leu⁸, Nle¹⁸, Tyr³⁴]hPTH(1-34)NH₂
Example 9: [D-Cha⁸, Nle¹⁸, Tyr³⁴]hPTH(1-34)NH₂
Example 10: [D-Phe⁸, Nle¹⁸, Tyr³⁴]hPTH(1-34)NH₂
10 Example 11: [D-Nal⁸, Nle¹⁸, Tyr³⁴]hPTH(1-34)NH₂
Example 12: [D-Abu⁸, Nle¹⁸, Tyr³⁴]hPTH(1-34)NH₂
Example 13: [D-Met⁸]hPTH(1-34)NH₂
Example 14: [Cha^{7,11}, D-Met⁸]hPTH(1-34)NH₂
Example 15: [D-Ile⁸]hPTH(1-34)NH₂
15 Example 16: [Cha^{7,11}, D-Ile⁸, Nle¹⁸, Tyr³⁴]hPTH(1-34)NH₂
Example 17: [D-Ile⁸, Nle¹⁸, Tyr³⁴]hPTH(1-34)NH₂
Example 18: [D-Leu⁸]hPTH(1-34)NH₂
Example 19: [Cha^{7,11}, D-Leu⁸, Nle¹⁸, Tyr³⁴]hPTH(1-34)NH₂
Example 20: [D-Val⁸]hPTH(1-34)NH₂
20 Example 21: [Cha^{7,11}, D-Val⁸, Nle¹⁸, Tyr³⁴]hPTH(1-34)NH₂
Example 22: [D-Val⁸, Nle¹⁸, Tyr³⁴]hPTH(1-34)NH₂
Example 23: [D-Cha⁸]hPTH(1-34)NH₂
Example 24: [Cha^{7,11}, D-Cha⁸, Nle¹⁸, Tyr³⁴]hPTH(1-34)NH₂
Example 25: [D-Ala⁸]hPTH(1-34)NH₂
25 Example 26: [Cha^{7,11}, D-Ala⁸, Nle¹⁸, Tyr³⁴]hPTH(1-34)NH₂
Example 27: [D-Ala⁸, Nle¹⁸, Tyr³⁴]hPTH(1-34)NH₂
Example 28: [D-Phe⁸]hPTH(1-34)NH₂
Example 29: [Cha^{7,11}, D-Phe⁸, Nle¹⁸, Tyr³⁴]hPTH(1-34)NH₂
Example 30: [D-Met⁸]hPTH(7-34)NH₂
30 Example 31: [D-Nal⁸]hPTH(1-34)NH₂
Example 32: [D-Trp⁸]hPTH(1-34)NH₂
Example 33: [Cha^{7,11}, D-Trp⁸, Nle¹⁸, Tyr³⁴]hPTH(1-34)NH₂
Example 34: [D-Trp⁸, Nle¹⁸, Tyr³⁴]hPTH(1-34)NH₂

- Example 35: [D-Abu⁸]hPTH(1-34)NH₂
- Example 36: [Cha^{7,11}, D-Abu⁸, Nle¹⁸, Tyr³⁴]hPTH(1-34)NH₂
- Example 37: [des-Met⁸]hPTH(1-34)NH₂
- Example 38: [Cha^{7,11}, des-Met⁸]hPTH(1-34)NH₂
- 5 Example 39: [Cha^{7,11}, des-Met⁸, des-Met¹⁸, Tyr³⁴]hPTH(1-34)NH₂
- Example 40: [des-Met⁸, des-Met¹⁸]hPTH(1-34)NH₂
- Example 41: [Cha^{7,11}, des-Met⁸, des-Met¹⁸]hPTH(1-34)NH₂
- Example 42: [des-Met⁸, Nle¹³, Tyr³⁴]hPTH(1-34)NH₂
- Example 43: [des-Met¹⁸]hPTH(1-34)NH₂
- 10 Example 44: [Cha^{7,11}, des-Met¹⁸]hPTH(1-34)NH₂
- Example 45: [Cha^{7,11}, des-Met¹⁸, Tyr³⁴]hPTH(1-34)NH₂
- Example 46: [D-Nle⁸, des-Met¹⁸, Tyr³⁴]hPTH(1-34)NH₂
- Example 47: [des-Glu⁶, Nle^{8,18}, Tyr³⁴]hPTH(1-34)NH₂
- Example 48: [des-Leu⁷, Nle^{8,18}, Tyr³⁴]hPTH(1-34)NH₂
- 15 Example 49: [des-His⁹, Nle^{8,18}, Tyr³⁴]hPTH(1-34)NH₂
- Example 50: [des-Asn¹⁰, Nle^{8,18}, Tyr³⁴]hPTH(1-34)NH₂
- Example 51: [des-Leu¹¹, Nle^{8,18}, Tyr³⁴]hPTH(1-34)NH₂
- Example 52: [des-Gly¹², Nle^{8,18}, Tyr³⁴]hPTH(1-34)NH₂
- Example 53: [des-Lys¹³, Nle^{8,18}, Tyr³⁴]hPTH(1-34)NH₂
- 20 Example 54: [des-His¹⁴, Nle^{8,18}, Tyr³⁴]hPTH(1-34)NH₂
- Example 55: [des-Leu¹⁵, Nle^{8,18}, Tyr³⁴]hPTH(1-34)NH₂
- Example 56: [des-Asn¹⁶, Nle^{8,18}, Tyr³⁴]hPTH(1-34)NH₂
- Example 57: [des-Ser¹⁷, Nle^{8,18}, Tyr³⁴]hPTH(1-34)NH₂
- Example 58: [des-Glu¹⁹, Nle^{8,18}, Tyr³⁴]hPTH(1-34)NH₂
- 25 Example 59: [des-Arg²⁰, Nle^{8,18}, Tyr³⁴]hPTH(1-34)NH₂
- Example 60: [des-Val²¹, Nle^{8,18}, Tyr³⁴]hPTH(1-34)NH₂
- Example 61: [des-Glu²², Nle^{8,18}, Tyr³⁴]hPTH(1-34)NH₂
- Example 62: [des-Glu⁶, Cha^{7,11}, Nle^{8,18}, Tyr³⁴]hPTH(1-34)NH₂
- Example 63: [des-Leu⁷, Nle^{8,18}, Cha¹¹, Tyr³⁴]hPTH(1-34)NH₂
- 30 Example 64: [Cha^{7,11}, des-His⁹, Nle^{8,18}, Tyr³⁴]hPTH(1-34)NH₂
- Example 65: [des-Glu⁶, Cha^{7,11}, D-Nle⁸, Nle¹⁸, Tyr³⁴]hPTH(1-34)NH₂
- Example 66: [des-Leu⁷, D-Nle⁸, Cha¹¹, Nle¹⁸, Tyr³⁴]hPTH(1-34)NH₂
- Example 67: [Cha^{7,11}, D-Nle⁸, des-His⁹, Nle¹⁸, Tyr³⁴]hPTH(1-34)NH₂

Example 68: [Cha^{7,11}, des-Met⁸, des-His⁹, des-Asn¹⁰]hPTH(1-34)NH₂

Example 69: [Cha^{7,11}, des-Ser¹⁷, des-Met¹⁸, des-Glu¹⁹]hPTH(1-34)NH₂

Example 70: [D-Met⁸, Nle¹⁸, Tyr³⁴]hPTH(1-34)NH₂

Example 71: [D-Met⁸, Tyr³⁴]hPTH(1-34)NH₂

5 Example 72: [D-Nle⁸, Nle¹⁸, Tyr³⁴]hPTH(7-34)NH₂

Example 73: [D-Nle⁸, Nle¹⁸]hPTH(7-34)NH₂

Example 74: [Ile⁵, D-Leu⁸]hPTHrP(1-34)NH₂

Example 75: [Ile⁵, D-Leu⁸, Trp²³]hPTHrP(1-34)NH₂

Example 76: [Ile⁵, des-Leu⁸, Trp²³]hPTHrP(1-34)NH₂

10 Example 77: [Ile⁵, des-Leu⁸]hPTHrP(1-34)NH₂

Example 78: [des-Leu⁸, Trp²³]hPTHrP(1-34)NH₂

Example 79: [Ile⁵, des-Leu¹⁸]hPTHrP(1-34)NH₂

Example 80: [Ile⁵, des-Leu¹⁸, Trp²³]hPTHrP(1-34)NH₂

Example 81: [des-Leu¹⁸, Trp²³]hPTHrP(1-34)NH₂

15 Example 82: [Ile⁵, D-Leu⁸, Glu^{22,25}, Leu^{23,28,31}, Lys^{26,30}, Aib²⁹]hPTHrP(1-34)NH₂

Example 83: [Ile⁵, D-Leu⁸, Glu^{22,25}, Trp²³, Lys^{26,30}, Leu^{28,31}, Aib²⁹]hPTHrP(1-34)NH₂

Example 84: [Ile⁵, D-Leu⁸, Glu^{22,25,29}, Leu^{23,28,31}, Lys^{26,30}]hPTHrP(1-34)NH₂

Example 85: [Ile⁵, D-Leu⁸, Glu^{22,25,29}, Trp²³, Lys^{26,30}, Leu^{28,31}]hPTHrP(1-34)NH₂

Example 86: [D-Leu⁸, Trp²³]hPTHrP(7-34)NH₂

20

CLAIMS

What is claimed is:

1. A PTH analogue or a truncated PTH analogue or a pharmaceutically acceptable salt thereof that selectively binds to the PTH2 receptor.

5 2. A PTH analogue or a truncated PTH analogue or a pharmaceutically acceptable salt thereof according to claim 1 where said analogue is a selective PTH2 receptor agonist.

3. A PTH analogue or a truncated PTH analogue or a pharmaceutically acceptable salt thereof according to claim 1 where said analogue is a selective PTH2
10 receptor antagonist.

4. A method of selectively binding a PTH2 receptor which comprises administering to a patient in need thereof an effective amount of an analogue according to claim 1 or a pharmaceutically-acceptable salt thereof.

5. A method of selectively eliciting an agonist response from the PTH2 receptor
15 which comprises administering to a patient in need thereof an effective amount of an analogue according to claim 2 or a pharmaceutically acceptable salt thereof.

6. A method of selectively eliciting an antagonist response from the PTH2 receptor which comprises administering to a patient in need thereof an effective amount of an analogue according to claim 3 or a pharmaceutically acceptable salt thereof.

20 7. An analogue according to claim 1 wherein said analogue is of formula (I),
(R¹R²)-A¹-A²-A³-A⁴-A⁵-A⁶-A⁷-A⁸-A⁹-A¹⁰-A¹¹-A¹²-A¹³-A¹⁴-A¹⁵-A¹⁶-A¹⁷-A¹⁸-A¹⁹-A²⁰-A²¹-A²²-A²³-A²⁴-
A²⁵-A²⁶-A²⁷-A²⁸-A²⁹-A³⁰-A³¹-A³²-A³³-A³⁴-A³⁵-A³⁶-A³⁷-A³⁸-R³,

(I)

or a pharmaceutically-acceptable salt thereof wherein

25 A¹ is a hydrophilic or a lipophilic amino acid;

A² is a lipophilic amino acid;

A³ is a hydrophilic or a lipophilic amino acid;

A⁴ is a hydrophilic amino acid

A⁵ is a hydrophilic or a lipophilic amino acid;

30 A⁶ is a hydrophilic amino acid or is deleted;

A⁷ is a hydrophilic or a lipophilic amino acid or is deleted;

A⁸ is a lipophilic amino acid or is deleted;

A⁹ is a hydrophilic amino acid or is deleted;

- A¹⁰ is a hydrophilic amino acid or is deleted;
A¹¹ is a hydrophilic or a lipophilic amino acid or is deleted;
A¹² is a hydrophilic or a lipophilic amino acid or is deleted;
A¹³ is a hydrophilic amino acid;
5 A¹⁴ is a hydrophilic amino acid or is deleted;
A¹⁵ is a lipophilic amino acid or is deleted;
A¹⁶ is a hydrophilic or a lipophilic amino acid or is deleted;
A¹⁷ is a hydrophilic or a lipophilic amino acid or is deleted;
A¹⁸ is a lipophilic amino acid or is deleted;
10 A¹⁹ is a hydrophilic or a lipophilic amino acid or is deleted;
A²⁰ is a hydrophilic amino acid or is deleted;
A²¹ is a hydrophilic or a lipophilic amino acid or is deleted;
A²² is a lipophilic or a hydrophilic amino acid or is deleted;
A²³ is a hydrophilic or a lipophilic amino acid;
15 A²⁴ is a hydrophilic or a lipophilic amino acid;
A²⁵ is a hydrophilic amino acid;
A²⁶ is a hydrophilic amino acid;
A²⁷ is a lipophilic or a hydrophilic amino acid;
A²⁸ is a lipophilic amino acid;
20 A²⁹ is a lipophilic or a hydrophilic amino acid;
A³⁰ is a hydrophilic or a lipophilic amino acid;
A³¹ is a lipophilic or a hydrophilic amino acid or is deleted;
A³² is a hydrophilic amino acid or is deleted;
A³³ is a hydrophilic amino acid or is deleted;
25 A³⁴ is a lipophilic amino acid or is deleted;
A³⁵ is a lipophilic amino acid or is deleted;
A³⁶ is a lipophilic or a hydrophilic amino acid or is deleted;
A³⁷ is a lipophilic amino acid or is deleted;
A³⁸ is a lipophilic or a hydrophilic amino acid or is deleted;
30 R¹ and R² are each independently selected from the group consisting of H, (C₁₋₃₀)alkyl, (C₂₋₃₀)alkenyl, phenyl-(C₁₋₃₀)alkyl, naphthyl(C₁₋₃₀)alkyl, hydroxy(C₁₋₃₀)alkyl, hydroxy(C₂₋₃₀)alkenyl, hydroxy-phenyl(C₁₋₃₀)alkyl or hydroxy-naphthyl(C₁₋₃₀)alkyl,

or one of R¹ or R² is COE¹ where E¹ is (C₁₋₃₀)alkyl, (C₂₋₃₀)alkenyl, phenyl(C₁₋₃₀)alkyl, naphthyl(C₁₋₃₀)alkyl, hydroxy(C₁₋₃₀)alkyl, hydroxy(C₂₋₃₀)alkenyl, hydroxy-phenyl(C₁₋₃₀)alkyl or hydroxy-naphthyl(C₁₋₃₀)alkyl; and

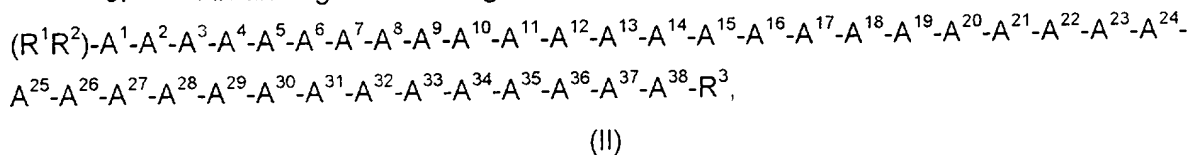
R³ is OH, NH₂, (C₁₋₃₀)alkoxy or NH-Y-CH₂-Z, where Y is a (C₁₋₃₀) hydrocarbon moiety

5 and Z is CO₂H or CONH₂;

provided that the compound is not PTH(1-34)R³, PTH(1-35)R³, PTH(1-36)R³, PTH(1-37)R³, or PTH(1-38)R³.

8. A method of selectively binding a PTH2 receptor which comprises administering to a patient in need thereof an effective amount of an analogue according to claim 7 or a pharmaceutically-acceptable salt thereof.

9. An analogue according to claim 1 of formula (II),



15 or a pharmaceutically-acceptable salt thereof wherein

A¹ is Ser, Ala, Dap, Thr, Aib or is deleted;

A² is Val, Leu, Ile, Phe, Nle, β-Nal, Aib, p-X-Phe, Acc, Cha, Met or is deleted;

A³ is Ser, Thr, Aib or is deleted;

A⁴ is Glu, Asp or is deleted;

20 A⁵ is Leu, Val, Nle, Ile, Cha, β-Nal, Trp, Pal, Acc, Phe, p-X-Phe or is deleted;

A⁶ is Gln, a hydrophilic amino acid or is deleted;

A⁷ is Leu, Val, Nle, Ile, Cha, β-Nal, Trp, Pal, Acc, Phe, p-X-Phe, a lipophilic amino acid, or is deleted;

25 A⁸ is Met, Nva, Leu, Val, Ile, Cha, Acc, Nle, p-X-Phe, Phe, β-Nal, Bpa, a lipophilic amino acid or is deleted;

A⁹ is His, a hydrophilic amino acid or is deleted;

A¹⁰ is Asn, a hydrophilic amino acid or is deleted;

A¹¹ is Leu, Val, Nle, Ile, Cha, β-Nal, Trp, Pal, Acc, Phe, p-X-Phe, a hydrophilic amino acid or is deleted;

30 A¹² is Gly, Acc, Aib, or is deleted;

A¹³ is Lys, Arg or HN-CH((CH₂)_nNH-R⁴)-C(O);

A¹⁴ is His or is deleted;

A¹⁵ is Leu, Val, Nle, Ile, Cha, β -Nal, Trp, Pal, Acc, Phe, p-X-Phe or is deleted;

A¹⁶ is Ser, Asn, Ala, Aib or is deleted;

A¹⁷ is Ser, Thr, Aib or is deleted;

A¹⁸ is Met, Nva, Leu, Val, Ile, Nle, p-X-Phe, Phe, β -Nal, Acc, Cha, Aib or is deleted;

5 A¹⁹ is Glu, Aib or is deleted;

A²⁰ is Arg, Lys, HN-CH((CH₂)_nNH-R⁴)-C(O) or is deleted;

A²¹ is Val, Leu, Ile, Phe, Nle, β -Nal, Aib, p-X-Phe, Acc, Cha, Met or is deleted;

A²² is Acc, Aib, Glu or is deleted;

A²³ is Trp, Acc, Phe, p-X-Phe, Aib, β -Nal or Cha;

10 A²⁴ is Leu, Acc, Ile, Val, Phe, β -Nal, Nle, Aib, p-X-Phe or Cha;

A²⁵ is Arg, Lys or HN-CH((CH₂)_nNH-R⁴)-C(O);

A²⁶ is Arg, Lys or HN-CH((CH₂)_nNH-R⁴)-C(O);

A²⁷ is Lys, Aib, Leu, hArg, Gln, Acc, Arg, Cha, Nle, Ile, Val, Phe, β -Nal, or p-X-Phe, where the Lys is optionally substituted on the ϵ -amino group by an acyl group;

15 A²⁸ is Leu, Acc, Cha, Ile, Val, Phe, Nle, β -Nal, Aib or p-X-Phe;

A²⁹ is Gln, Acc or Aib;

A³⁰ is Asp, Lys, Arg or is deleted;

A³¹ is Val, Leu, Nle, Acc, Cha, Phe, Ile, β -Nal, Aib, p-X-Phe or is deleted;

A³² is His or is deleted;

20 A³³ is Asn or is deleted;

A³⁴ is Phe, Tyr, Amp, Aib, β -Nal, Cha, Nle, Leu, Ile, Acc, p-X-Phe or is deleted;

A³⁵ is Val, Leu, Nle, Acc, Cha, Phe, Ile, β -Nal, Aib, p-X-Phe or is deleted;

A³⁶ is Ala, Val, Aib, Acc, Nva, Abu or is deleted;

A³⁷ is Leu, Val, Nle, Ile, Cha, β -Nal, Trp, Pal, Acc, Phe, p-X-Phe, a lipophilic amino acid, or

25 is deleted;

A³⁸ is Gly, Acc, Aib, or is deleted;

where X for each occurrence is independently selected from the group consisting of OH, a halo and CH₃;

R¹ and R² are each independently selected from the group consisting of H, (C₁₋₃₀)alkyl, (C₂₋₃₀)alkenyl, phenyl-(C₁₋₃₀)alkyl, naphthyl(C₁₋₃₀)alkyl, hydroxy(C₁₋₃₀)alkyl, hydroxy(C₂₋₃₀)alkenyl, hydroxy-phenyl(C₁₋₃₀)alkyl or hydroxy-naphthyl(C₁₋₃₀)alkyl;

30

or one of R¹ or R² is COE¹ where E¹ is (C₁₋₃₀)alkyl, (C₂₋₃₀)alkenyl, phenyl(C₁₋₃₀)alkyl, naphthyl(C₁₋₃₀)alkyl, hydroxy(C₁₋₃₀)alkyl, hydroxy(C₂₋₃₀)alkenyl, hydroxy-phenyl(C₁₋₃₀)alkyl or hydroxy-naphthyl(C₁₋₃₀)alkyl;

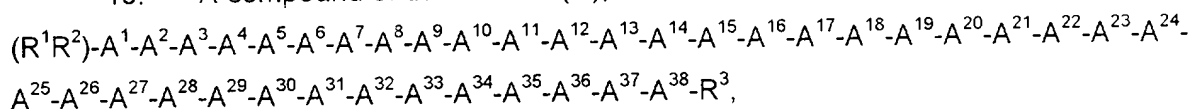
R³ is OH, NH₂, (C₁₋₃₀)alkoxy or NH-Y-CH₂-Z, where Y is a (C₁₋₃₀) hydrocarbon moiety and Z is CO₂H or CONH₂;

n for each occurrence is independently an integer from 1 to 5; and

R⁴ for each occurrence is independently (C_{1-C30})alkyl, (C_{1-C30})acyl or -C((NH)(NH₂));

provided that the compound is not PTH(1-34)R³, PTH(1-35)R³, PTH(1-36)R³, PTH(1-37)R³, or PTH(1-38)R³.

10 10. A compound of the formula (III),



(III)

or a pharmaceutically-acceptable salt thereof wherein

15 A¹ is Ser, Ala, Dap, Thr, Aib or is deleted;

A² is Val, Leu, Ile, Phe, Nle, β-Nal, Aib, p-X-Phe, Acc, Cha, Met or is deleted;

A³ is Ser, Thr, Aib or is deleted;

A⁴ is Glu, Asp or is deleted;

A⁵ is Leu, Val, Nle, Ile, Cha, β-Nal, Trp, Pal, Acc, Phe, p-X-Phe or is deleted;

20 A⁶ is Gln, a hydrophilic amino acid or is deleted;

A⁷ is Leu, Val, Nle, Ile, Cha, β-Nal, Trp, Pal, Acc, Phe, p-X-Phe, a lipophilic amino acid, or is deleted;

A⁸ is Met, Nva, Leu, Val, Ile, Cha, Acc, Nle, p-X-Phe, Phe, β-Nal, Bpa, a lipophilic amino acid or is deleted;

25 A⁹ is His, a hydrophilic amino acid or is deleted;

A¹⁰ is Asn, a hydrophilic amino acid or is deleted;

A¹¹ is Leu, Val, Nle, Ile, Cha, β-Nal, Trp, Pal, Acc, Phe, p-X-Phe, a hydrophilic amino acid or is deleted;

A¹² is Gly, Acc, Aib, or is deleted;

30 A¹³ is Lys, Arg or HN-CH((CH₂)_nNH-R⁴)-C(O);

A¹⁴ is His or is deleted;

A¹⁵ is Leu, Val, Nle, Ile, Cha, β-Nal, Trp, Pal, Acc, Phe, p-X-Phe or is deleted;

- A¹⁶ is Ser, Asn, Ala, Aib or is deleted;
A¹⁷ is Ser, Thr, Aib or is deleted;
A¹⁸ is Met, Nva, Leu, Val, Ile, Nle, p-X-Phe, Phe, β-Nal, Acc, Cha, Aib or is deleted;
A¹⁹ is Glu, Aib or is deleted;
5 A²⁰ is Arg, Lys, HN-CH((CH₂)_nNH-R⁴)-C(O) or is deleted;
A²¹ is Val, Leu, Ile, Phe, Nle, β-Nal, Aib, p-X-Phe, Acc, Cha, Met or is deleted;
A²² is Acc, Aib, Glu or is deleted;
A²³ is Trp, Acc, Phe, p-X-Phe, Aib, β-Nal or Cha;
A²⁴ is Leu, Acc, Ile, Val, Phe, β-Nal, Nle, Aib, p-X-Phe or Cha;
10 A²⁵ is Arg, Lys or HN-CH((CH₂)_nNH-R⁴)-C(O);
A²⁶ is Arg, Lys or HN-CH((CH₂)_nNH-R⁴)-C(O);
A²⁷ is Lys, Aib, Leu, hArg, Gln, Acc, Arg, Cha, Nle, Ile, Val, Phe, β-Nal, or p-X-Phe, where
the Lys is optionally substituted on the ε-amino group by an acyl group;
A²⁸ is Leu, Acc, Cha, Ile, Val, Phe, Nle, β-Nal, Aib or p-X-Phe;
15 A²⁹ is Gln, Acc or Aib;
A³⁰ is Asp, Lys, Arg or is deleted;
A³¹ is Val, Leu, Nle, Acc, Cha, Phe, Ile, β-Nal, Aib, p-X-Phe or is deleted;
A³² is His or is deleted;
A³³ is Asn or is deleted;
20 A³⁴ is Phe, Tyr, Amp, Aib, β-Nal, Cha, Nle, Leu, Ile, Acc, p-X-Phe or is deleted;
A³⁵ is Val, Leu, Nle, Acc, Cha, Phe, Ile, β-Nal, Aib, p-X-Phe or is deleted;
A³⁶ is Ala, Val, Aib, Acc, Nva, Abu or is deleted;
A³⁷ is Leu, Val, Nle, Ile, Cha, β-Nal, Trp, Pal, Acc, Phe, p-X-Phe, a lipophilic amino acid, or
is deleted;
25 A³⁸ is Gly, Acc, Aib, or is deleted;
where X for each occurrence is independently selected from the group consisting of
OH, a halo and CH₃;
R¹ and R² are each independently selected from the group consisting of H, (C₁-
30 (C₂₋₃₀)alkenyl, phenyl-(C₁₋₃₀)alkyl, naphthyl(C₁₋₃₀)alkyl, hydroxy(C₁₋₃₀)alkyl,
hydroxy(C₂₋₃₀)alkenyl, hydroxy-phenyl(C₁₋₃₀)alkyl or hydroxy-naphthyl(C₁₋₃₀)alkyl;

or one of R¹ or R² is COE¹ where E¹ is (C₁₋₃₀)alkyl, (C₂₋₃₀)alkenyl, phenyl(C₁₋₃₀)alkyl, naphthyl(C₁₋₃₀)alkyl, hydroxy(C₁₋₃₀)alkyl, hydroxy(C₂₋₃₀)alkenyl, hydroxy-phenyl(C₁₋₃₀)alkyl or hydroxy-naphthyl(C₁₋₃₀)alkyl;

R³ is OH, NH₂, (C₁₋₃₀)alkoxy or NH-Y-CH₂-Z, where Y is a (C₁₋₃₀) hydrocarbon moiety and Z is CO₂H or CONH₂;

n for each occurrence is independently an integer from 1 to 5; and

R⁴ for each occurrence is independently (C_{1-C30})alkyl, (C_{1-C30})acyl or -C((NH)(NH₂));

provided that when A⁸ is not a lipophilic D-amino acid or is not deleted then at least one of A⁶, A⁷, A⁹, A¹⁰, A¹¹ and A¹² is a D-amino acid or at least one of A⁶, A⁷, A⁹, A¹⁰, A¹¹, A¹², A¹³.

10 A¹⁴, A¹⁵, A¹⁶, A¹⁷, A¹⁸, A¹⁹, A²⁰, A²¹ and A²² is deleted;

and further provided that when the compound contains a D-amino acid then A³⁶ is deleted

11. A compound according to claim 10 wherein said compound is

[D-Nle⁸, Nle¹⁸, Tyr³⁴]hPTH(1-34)NH₂,

[D-Nle⁸]hPTH(1-34)NH₂.

15 [D-Leu⁸, Nle¹⁸, Tyr³⁴]hPTH(1-34)NH₂,

[D-Cha⁸, Nle¹⁸, Tyr³⁴]hPTH(1-34)NH₂,

[D-Phe⁸, Nle¹⁸, Tyr³⁴]hPTH(1-34)NH₂,

[D-Nal⁸, Nle¹⁸, Tyr³⁴]hPTH(1-34)NH₂,

[D-Abu⁸, Nle¹⁸, Tyr³⁴]hPTH(1-34)NH₂,

20 [D-Met⁸]hPTH(1-34)NH₂,

[Cha^{7,11}, D-Met⁸]hPTH(1-34)NH₂,

[D-Ile⁸]hPTH(1-34)NH₂,

[Cha^{7,11}, D-Ile⁸, Nle¹⁸, Tyr³⁴]hPTH(1-34)NH₂,

[D-Ile⁸, Nle¹⁸, Tyr³⁴]hPTH(1-34)NH₂,

25 [D-Leu⁸]hPTH(1-34)NH₂,

[Cha^{7,11}, D-Leu⁸, Nle¹⁸, Tyr³⁴]hPTH(1-34)NH₂,

[D-Val⁸]hPTH(1-34)NH₂,

[Cha^{7,11}, D-Val⁸, Nle¹⁸, Tyr³⁴]hPTH(1-34)NH₂,

[D-Val⁸, Nle¹⁸, Tyr³⁴]hPTH(1-34)NH₂,

30 [D-Cha⁸]hPTH(1-34)NH₂.

[Cha^{7,11}, D-Cha⁸, Nle¹⁸, Tyr³⁴]hPTH(1-34)NH₂,

[D-Ala⁸]hPTH(1-34)NH₂,

[Cha^{7,11}, D-Ala⁸, Nle¹⁸, Tyr³⁴]hPTH(1-34)NH₂,

- [D-Ala⁸, Nle¹⁸, Tyr³⁴]hPTH(1-34)NH₂,
 [D-Phe⁸]hPTH(1-34)NH₂,
 [Cha^{7,11}, D-Phe⁸, Nle¹⁸, Tyr³⁴]hPTH(1-34)NH₂,
 [D-Nal⁸]hPTH(1-34)NH₂,
 5 [D-Trp⁸]hPTH(1-34)NH₂,
 [Cha^{7,11}, D-Trp⁸, Nle¹⁸, Tyr³⁴]hPTH(1-34)NH₂,
 [D-Trp⁸, Nle¹⁸, Tyr³⁴]hPTH(1-34)NH₂,
 [D-Abu⁸]hPTH(1-34)NH₂,
 [Cha^{7,11}, D-Abu⁸, Nle¹⁸, Tyr³⁴]hPTH(1-34)NH₂,
 10 [D-Nle⁸, Nle¹⁸]hPTH(1-34)NH₂,
 [des-Met⁸]hPTH(1-34)NH₂,
 [Cha^{7,11}, des-Met⁸]hPTH(1-34)NH₂,
 [Cha^{7,11}, des-Met⁸, des-Met¹⁸, Tyr³⁴]hPTH(1-34)NH₂,
 [des-Met⁸, des-Met¹⁸]hPTH(1-34)NH₂,
 15 [Cha^{7,11}, des-Met⁸, des-Met¹⁸]hPTH(1-34)NH₂,
 [des-Met⁸, Nle¹⁸, Tyr³⁴]hPTH(1-34)NH₂,
 [des-Met¹⁸]hPTH(1-34)NH₂,
 [Cha^{7,11}, des-Met¹⁸]hPTH(1-34)NH₂,
 [Cha^{7,11}, des-Met¹⁸, Tyr³⁴]hPTH(1-34)NH₂,
 20 [D-Nle⁸, des-Met¹⁸, Tyr³⁴]hPTH(1-34)NH₂,
 [des-Glu⁶, Nle^{8,18}, Tyr³⁴]hPTH(1-34)NH₂,
 [des-Leu⁷, Nle^{8,18}, Tyr³⁴]hPTH(1-34)NH₂,
 [des-His⁹, Nle^{8,18}, Tyr³⁴]hPTH(1-34)NH₂,
 [des-Asn¹⁰, Nle^{8,18}, Tyr³⁴]hPTH(1-34)NH₂,
 25 [des-Leu¹¹, Nle^{8,18}, Tyr³⁴]hPTH(1-34)NH₂,
 [des-Gly¹², Nle^{8,18}, Tyr³⁴]hPTH(1-34)NH₂,
 [des-Lys¹³, Nle^{8,18}, Tyr³⁴]hPTH(1-34)NH₂,
 [des-His¹⁴, Nle^{8,18}, Tyr³⁴]hPTH(1-34)NH₂,
 [des-Leu¹⁵, Nle^{8,18}, Tyr³⁴]hPTH(1-34)NH₂,
 30 [des-Asn¹⁶, Nle^{8,18}, Tyr³⁴]hPTH(1-34)NH₂,
 [des-Ser¹⁷, Nle^{8,18}, Tyr³⁴]hPTH(1-34)NH₂,
 [des-Glu¹⁹, Nle^{8,18}, Tyr³⁴]hPTH(1-34)NH₂,
 [des-Arg²⁰, Nle^{8,18}, Tyr³⁴]hPTH(1-34)NH₂,

- [des-Val²¹, Nle^{8,18}, Tyr³⁴]hPTH(1-34)NH₂,
 [des-Glu²², Nle^{8,18}, Tyr³⁴]hPTH(1-34)NH₂,
 [des-Glu⁶, Cha^{7,11}, Nle^{8,18}, Tyr³⁴]hPTH(1-34)NH₂,
 [des-Leu⁷, Nle^{8,18}, Cha¹¹, Tyr³⁴]hPTH(1-34)NH₂,
 5 [Cha^{7,11}, des-His⁹, Nle^{8,18}, Tyr³⁴]hPTH(1-34)NH₂,
 [des-Glu⁶, Cha^{7,11}, D-Nle⁸, Nle¹⁸, Tyr³⁴]hPTH(1-34)NH₂,
 [des-Leu⁷, D-Nle⁸, Cha¹¹, Nle¹⁸, Tyr³⁴]hPTH(1-34)NH₂,
 [Cha^{7,11}, D-Nle⁸, des-His⁹, Nle¹⁸, Tyr³⁴]hPTH(1-34)NH₂,
 [Cha^{7,11}, D-Nle⁸, Nle¹⁸, Tyr³⁴]hPTH(1-31)NH₂,
 10 [Cha^{7,11}, des-Met⁸, Nle¹⁸, Tyr³⁴]hPTH(1-34)NH₂,
 [Cha^{7,11}, D-Nle⁸, des-Met¹⁸, Tyr³⁴]hPTH(1-34)NH₂,
 [Cha^{7,11}, des-Met⁸, des-His⁹, des-Asn¹⁰]hPTH(1-34)NH₂,
 [Cha^{7,11}, des-Ser¹⁷, des-Met¹⁸, des-Glu¹⁹]hPTH(1-34)NH₂,
 [D-Met⁸, Nle¹⁸, Tyr³⁴]hPTH(1-34)NH₂,
 15 [D-Met⁸, Tyr³⁴]hPTH(1-34)NH₂,
 [D-Bpa⁸, Tyr³⁴]hPTH(1-34)NH₂,
 [D-Nle⁸, Nle¹⁸, Tyr³⁴]hPTH(7-34)NH₂,
 [D-Nle⁸, Nle¹⁸]hPTH(7-34)NH₂ or
 [D-Met⁸]hPTH(7-34)NH₂.
 20 12. A compound according to claim 11 wherein said compound is
 [Cha^{7,11}, des-Met⁸, Nle¹⁸, Tyr³⁴]hPTH-(1-34)NH₂,
 [Cha^{7,11}, D-Nle⁸, des-Met¹⁸, Tyr³⁴]hPTH-(1-34)NH₂,
 [Cha^{7,11}, D-Nle⁸, Nle¹⁸, Tyr³⁴]hPTH-(1-34)NH₂,
 [D-Nle⁸, Nle¹⁸, Tyr³⁴]hPTH(1-34)NH₂ or [D-Bpa⁸, Tyr³⁴]hPTH(1-34)NH₂.
 25 13. A PTHrP analogue of formula (IV) that selectively binds to the PTH2
 receptor,
 (R¹R²)-A¹-A²-A³-A⁴-A⁵-A⁶-A⁷-A⁸-A⁹-A¹⁰-A¹¹-A¹²-A¹³-A¹⁴-A¹⁵-A¹⁶-A¹⁷-A¹⁸-A¹⁹-A²⁰-A²¹-A²²-A²³-A²⁴-
 A²⁵-A²⁶-A²⁷-A²⁸-A²⁹-A³⁰-A³¹-A³²-A³³-A³⁴-A³⁵-A³⁶-A³⁷-A³⁸-R³,
 (IV)
 30 or a pharmaceutically acceptable salt thereof, wherein
 A¹ is Ala, Ser, Dap, Thr, Aib or is deleted;
 A² is Val or is deleted;
 A³ is Ser, Aib, Thr or is deleted;

A⁴ is Glu, Asp or is deleted;

A⁵ is His, Ile, Acc, Val, Nle, Phe, Leu, p-X-Phe, β-Nal, Aib, Cha or is deleted;

A⁶ is Gln, a hydrophilic amino acid or is deleted;

A⁷ is Leu, Val, Cha, Nle, β-Nal, Trp, Pal, Acc, Phe, p-X-Phe, Aib, a lipophilic amino acid or is

5 deleted;

A⁸ is Leu, Met, Acc, Cha, Aib, Nle, Phe, Ile, Val, β-Nal, p-X-Phe, a lipophilic amino acid or is deleted;

A⁹ is His, a hydrophilic amino acid or is deleted;

A¹⁰ is Asp, Asn, a hydrophilic amino acid or is deleted;

10 A¹¹ is Lys, Arg, Leu, Cha, Aib, p-X-Phe, Ile, Val, Nle, Acc, Phe, β-Nal, HN-CH((CH₂)_nNH-R⁴)-C(O), a lipophilic D-amino acid, a hydrophilic amino acid or is deleted;

A¹² is Gly, Acc, Aib or is deleted;

A¹³ is Lys, Arg, HN-CH((CH₂)_nNH-R⁴)-C(O) or is deleted;

A¹⁴ is Ser, His or is deleted;

15 A¹⁵ is Ile, Acc, Cha, Leu, Phe, Nle, β-Nal, Trp, p-X-Phe, Val, Aib or is deleted;

A¹⁶ is Gln, Aib or is deleted;

A¹⁷ is Asp, Aib or is deleted;

A¹⁸ is Leu, Aib, Acc, Cha, Phe, Ile, Nle, β-Nal, Val, p-X-Phe or is deleted;

A¹⁹ is Arg, Lys, Aib, HN-CH((CH₂)_nNH-R⁴)-C(O) or is deleted;

20 A²⁰ is Arg, Lys, HN-CH((CH₂)_nNH-R⁴)-C(O) or is deleted;

A²¹ is Arg, Lys, HN-CH((CH₂)_nNH-R⁴)-C(O) or is deleted;

A²² is Phe, Glu, Aib, Acc, p-X-Phe, β-Nal, Val, Leu, Ile, Nle or Cha;

A²³ is Phe, Leu, Lys, Acc, Cha, β-Nal, Aib, Nle, Ile, p-X-Phe, Val or Trp;

A²⁴ is Leu, Lys, Acc, Nle, Ile, Val, Phe, β-Nal, Aib, p-X-Phe, Arg or Cha;

25 A²⁵ is His, Lys, Aib, Acc, Arg or Glu;

A²⁶ is His, Aib, Acc, Arg or Lys;

A²⁷ is Leu, Lys, Acc, Arg, Ile, Val, Phe, Aib, Nle, β-Nal, p-X-Phe or Cha;

A²⁸ is Ile, Leu, Lys, Acc, Cha, Val, Phe, p-X-Phe, Nle, β-Nal, Aib or is deleted;

A²⁹ is Ala, Glu, Acc, Aib or is deleted;

30 A³⁰ is Glu, Leu, Nle, Cha, Aib, Acc, Lys, Arg or is deleted;

A³¹ is Ile, Leu, Cha, Lys, Acc, Phe, Val, Nle, β-Nal, Arg or is deleted;

A³² is His or is deleted;

A³³ is Thr, Ser or is deleted;

A³⁴ is Ala, Phe, Tyr, Cha, Val, Ile, Leu, Nle, β-Nal, Aib, Acc or is deleted;

A³⁵ is Glu, Asp or is deleted;

A³⁶ is Ile, Acc, Cha, Leu, Phe, Nle, β-Nal, Trp, p-X-Phe, Val, Aib or is deleted;

5 A³⁷ is Arg, Lys, HN-CH((CH₂)_nNH-R⁴)-C(O) or is deleted;

A³⁸ is Ala, Phe, Tyr, Cha, Val, Ile, Leu, Nle, β-Nal, Aib, Acc or is deleted;

R¹ and R² are each independently selected from the group consisting of H, (C₁₋₃₀)alkyl, (C₂₋₃₀)alkenyl, phenyl-(C₁₋₃₀)alkyl, naphthyl(C₁₋₃₀)alkyl, hydroxy(C₁₋₃₀)alkyl, hydroxy(C₂₋₃₀)alkenyl, hydroxy-phenyl(C₁₋₃₀)alkyl or hydroxy-naphthyl(C₁₋₃₀)alkyl

10 or one of R¹ or R² is COE¹ where E¹ is (C₁₋₃₀)alkyl, (C₂₋₃₀)alkenyl, phenyl(C₁₋₃₀)alkyl, naphthyl(C₁₋₃₀)alkyl, hydroxy(C₁₋₃₀)alkyl, hydroxy(C₂₋₃₀)alkenyl, hydroxy-phenyl(C₁₋₃₀)alkyl or hydroxy-naphthyl(C₁₋₃₀)alkyl;

R³ is OH, NH₂, (C₁₋₃₀)alkoxy or NH-Y-CH₂-Z, where Y is a (C₁₋₃₀) hydrocarbon moiety and Z is CO₂H or CONH₂;

15 n for each occurrence is independently an integer from 1 to 5; and

R⁴ for each occurrence is independently (C₁-C₃₀)alkyl, (C₁-C₃₀)acyl or -C((NH)(NH₂)); provided that the compound is not PTHrP(1-34)R³, PTHrP(1-35)R³, PTHrP(1-36)R³, PTHrP(1-37)R³ or PTHrP(1-38)R³,

20 and further provided that the compound is not [Ile⁵, Trp²³]PTHrP(1-36) or [Trp²³]PTHrP(1-36).

14. A compound of formula (V),

(R¹R²)-A¹-A²-A³-A⁴-A⁵-A⁶-A⁷-A⁸-A⁹-A¹⁰-A¹¹-A¹²-A¹³-A¹⁴-A¹⁵-A¹⁶-A¹⁷-A¹⁸-A¹⁹-A²⁰-A²¹-A²²-A²³-A²⁴-A²⁵-A²⁶-A²⁷-A²⁸-A²⁹-A³⁰-A³¹-A³²-A³³-A³⁴-A³⁵-A³⁶-A³⁷-A³⁸-R³,

(V)

25 or a pharmaceutically acceptable salt thereof, wherein

A¹ is Ala, Ser, Dap, Thr, Aib or is deleted;

A² is Val or is deleted;

A³ is Ser, Aib, Thr or is deleted;

A⁴ is Glu, Asp or is deleted;

30 A⁵ is His, Ile, Acc, Val, Nle, Phe, Leu, p-X-Phe, β-Nal, Aib, Cha or is deleted;

A⁶ is Gln, a hydrophilic amino acid or is deleted;

A⁷ is Leu, Val, Cha, Nle, β-Nal, Trp, Pal, Acc, Phe, p-X-Phe, Aib, a lipophilic amino acid or is deleted;

- A^8 is Leu, Met, Acc, Cha, Aib, Nle, Phe, Ile, Val, β -Nal, p-X-Phe, a lipophilic amino acid or is deleted;
- A^9 is His, a hydrophilic amino acid or is deleted;
- A^{10} is Asp, Asn, a hydrophilic amino acid or is deleted;
- 5 A^{11} is Lys, Arg, Leu, Cha, Aib, p-X-Phe, Ile, Val, Nle, Acc, Phe, β -Nal, $\text{HN-CH}((\text{CH}_2)_n\text{NH-R}^4)\text{-C(O)}$, a lipophilic D-amino acid, a hydrophilic amino acid or is deleted;
- A^{12} is Gly, Acc, Aib or is deleted;
- A^{13} is Lys, Arg, $\text{HN-CH}((\text{CH}_2)_n\text{NH-R}^4)\text{-C(O)}$ or is deleted;
- A^{14} is Ser, His or is deleted;
- 10 A^{15} is Ile, Acc, Cha, Leu, Phe, Nle, β -Nal, Trp, p-X-Phe, Val, Aib or is deleted;
- A^{16} is Gln, Aib or is deleted;
- A^{17} is Asp, Aib or is deleted;
- A^{18} is Leu, Aib, Acc, Cha, Phe, Ile, Nle, β -Nal, Val, p-X-Phe or is deleted;
- A^{19} is Arg, Lys, Aib, $\text{HN-CH}((\text{CH}_2)_n\text{NH-R}^4)\text{-C(O)}$ or is deleted;
- 15 A^{20} is Arg, Lys, $\text{HN-CH}((\text{CH}_2)_n\text{NH-R}^4)\text{-C(O)}$ or is deleted;
- A^{21} is Arg, Lys, $\text{HN-CH}((\text{CH}_2)_n\text{NH-R}^4)\text{-C(O)}$ or is deleted;
- A^{22} is Phe, Glu, Aib, Acc, p-X-Phe, β -Nal, Val, Leu, Ile, Nle or Cha;
- A^{23} is Phe, Leu, Lys, Acc, Cha, β -Nal, Aib, Nle, Ile, p-X-Phe, Val or Trp;
- A^{24} is Leu, Lys, Acc, Nle, Ile, Val, Phe, β -Nal, Aib, p-X-Phe, Arg or Cha;
- 20 A^{25} is His, Lys, Aib, Acc, Arg or Glu;
- A^{26} is His, Aib, Acc, Arg or Lys;
- A^{27} is Leu, Lys, Acc, Arg, Ile, Val, Phe, Aib, Nle, β -Nal, p-X-Phe or Cha;
- A^{28} is Ile, Leu, Lys, Acc, Cha, Val, Phe, p-X-Phe, Nle, β -Nal, Aib or is deleted;
- A^{29} is Ala, Glu, Acc, Aib or is deleted;
- 25 A^{30} is Glu, Leu, Nle, Cha, Aib, Acc, Lys, Arg or is deleted;
- A^{31} is Ile, Leu, Cha, Lys, Acc, Phe, Val, Nle, β -Nal, Arg or is deleted;
- A^{32} is His or is deleted;
- A^{33} is Thr, Ser or is deleted;
- A^{34} is Ala, Phe, Tyr, Cha, Val, Ile, Leu, Nle, β -Nal, Aib, Acc or is deleted;
- 30 A^{35} is Glu, Asp or is deleted;
- A^{36} is Ile, Acc, Cha, Leu, Phe, Nle, β -Nal, Trp, p-X-Phe, Val, Aib or is deleted;
- A^{37} is Arg, Lys, $\text{HN-CH}((\text{CH}_2)_n\text{NH-R}^4)\text{-C(O)}$ or is deleted;

A³⁸ is Ala, Phe, Tyr, Cha, Val, Ile, Leu, Nle, β-Nal, Aib, Acc or is deleted;

R¹ and R² are each independently selected from the group consisting of H, (C₁₋₃₀)alkyl, (C₂₋₃₀)alkenyl, phenyl-(C₁₋₃₀)alkyl, naphthyl(C₁₋₃₀)alkyl, hydroxy(C₁₋₃₀)alkyl, hydroxy(C₂₋₃₀)alkenyl, hydroxy-phenyl(C₁₋₃₀)alkyl or hydroxy-naphthyl(C₁₋₃₀)alkyl;

5 or one of R¹ or R² is COE¹ where E¹ is (C₁₋₃₀)alkyl, (C₂₋₃₀)alkenyl, phenyl(C₁₋₃₀)alkyl, naphthyl(C₁₋₃₀)alkyl, hydroxy(C₁₋₃₀)alkyl, hydroxy(C₂₋₃₀)alkenyl, hydroxy-phenyl(C₁₋₃₀)alkyl or hydroxy-naphthyl(C₁₋₃₀)alkyl;

R³ is OH, NH₂, (C₁₋₃₀)alkoxy or NH-Y-CH₂-Z, where Y is a (C₁₋₃₀) hydrocarbon moiety and Z is CO₂H or CONH₂;

10 n for each occurrence is independently an integer from 1 to 5; and

R⁴ for each occurrence is independently (C₁-C₃₀)alkyl, (C₁-C₃₀)acyl or -C((NH)(NH₂));

provided that when A⁸ is not a lipophilic D-amino acid or is not deleted then at least one of A⁶, A⁷, A⁹, A¹⁰, A¹¹ and A¹² is a D-amino acid or at least one of A⁶, A⁷, A⁹, A¹⁰, A¹¹, A¹², A¹³, A¹⁴, A¹⁵, A¹⁶, A¹⁷, A¹⁸, A¹⁹, A²⁰, A²¹ and A²² is deleted.

15 15. A compound according to claim 14 wherein said compound is

[Ile⁵, D-Leu⁸]hPTHrP(1-34)NH₂,

[Ile⁵, D-Leu⁸, Trp²³]hPTHrP(1-34)NH₂,

[Ile⁵, des-Leu⁸, Trp²³]hPTHrP(1-34)NH₂,

[Ile⁵, des-Leu⁸]hPTHrP(1-34)NH₂,

20 [des-Leu⁸, Trp²³]hPTHrP(1-34)NH₂,

[Ile⁵, des-Leu¹⁸]hPTHrP(1-34)NH₂,

[Ile⁵, des-Leu¹⁸, Trp²³]hPTHrP(1-34)NH₂,

[des-Leu¹⁸, Trp²³]hPTHrP(1-34)NH₂,

[Ile⁵, D-Leu⁸, Glu^{22,25}, Leu^{23,28,31}, Lys^{26,30}, Aib²⁹]hPTHrP(1-34)NH₂,

25 [Ile⁵, D-Leu⁸, Glu^{22,25}, Trp²³, Lys^{26,30}, Leu^{28,31}, Aib²⁹]hPTHrP(1-34)NH₂,

[Ile⁵, D-Leu⁸, Glu^{22,25,29}, Leu^{23,28,31}, Lys^{26,30}]hPTHrP(1-34)NH₂,

[Ile⁵, D-Leu⁸, Glu^{22,25,29}, Trp²³, Lys^{26,30}, Leu^{28,31}]hPTHrP(1-34)NH₂ or

[D-Leu⁸, Trp²³]hPTHrP(7-34)NH₂.

30 16. A method of selectively binding the PTH2 receptor which comprises administering to a patient in need thereof an analogue according to claim 9 or a pharmaceutically acceptable salt thereof.

17. A method of selectively binding the PTH2 receptor which comprises administering to a patient in need thereof a compound according to claim 10 or a pharmaceutically acceptable salt thereof.

18. A method of selectively binding the PTH2 receptor which comprises
5 administering to a patient in need thereof a compound according to claim 11 or a pharmaceutically acceptable salt thereof.

19. A method of selectively binding a PTH2 receptor which comprises administering to a patient in need thereof a compound according to claim 12 or a pharmaceutically acceptable salt thereof.

10 20. A method of selectively binding a PTH2 receptor which comprises administering to a patient in need thereof an analogue according to claim 13 or a pharmaceutically acceptable salt thereof.

21 A method of selectively binding a PTH2 receptor which comprises administering to a patient in need thereof a compound according to claim 14 or a
15 pharmaceutically acceptable salt thereof.

22. A method of selectively binding a PTH2 receptor which comprises administering to a patient in need thereof a compound according to claim 15 or a pharmaceutically acceptable salt thereof.

23. A pharmaceutical composition comprising an analogue according to claim 9
20 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

24. A pharmaceutical composition comprising a compound according to claim 10 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

25. A pharmaceutical composition comprising a compound according to claim 11 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

25 26. A pharmaceutical composition comprising a compound according to claim 12 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

27. A pharmaceutical composition comprising an analogue according to claim 13 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier

28. A pharmaceutical composition comprising a compound according to claim 14
30 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

29. A pharmaceutical composition comprising a compound according to claim 15 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

30. A method of treating a medical disorder that results from altered or excessive action of the PTH2 receptor, which comprises administering to a patient in need thereof an effective amount of an analogue according to claim 7, sufficient to inhibit the activation of the PTH2 receptor of said patient.

5 31. A method of treating a medical disorder that results from altered or excessive action of the PTH2 receptor, which comprises administering to a patient in need thereof an effective amount of an analogue according to claim 9, sufficient to inhibit the activation of the PTH2 receptor of said patient.

10 32. A method of treating a medical disorder that results from altered or excessive action of the PTH2 receptor, which comprises administering to a patient in need thereof an effective amount of a compound according to claim 10, sufficient to inhibit the activation of the PTH2 receptor of said patient.

15 33. A method of treating a medical disorder that results from altered or excessive action of the PTH2 receptor, which comprises administering to a patient in need thereof an effective amount of a compound according to claim 11, sufficient to inhibit the activation of the PTH2 receptor of said patient.

20 34. A method of treating a medical disorder that results from altered or excessive action of the PTH2 receptor, which comprises administering to a patient in need thereof an effective amount of a compound according to claim 12, sufficient to inhibit the activation of the PTH2 receptor of said patient.

25 35. A method of treating a medical disorder that results from altered or excessive action of the PTH2 receptor, which comprises administering to a patient in need thereof an effective amount of an analogue according to claim 13, sufficient to inhibit the activation of the PTH2 receptor of said patient.

30 36. A method of treating a medical disorder that results from altered or excessive action of the PTH2 receptor, which comprises administering to a patient in need thereof an effective amount of a compound according to claim 14, sufficient to inhibit the activation of the PTH2 receptor of said patient.

37. A method of treating a medical disorder that results from altered or excessive action of the PTH2 receptor, which comprises administering to a patient in need thereof an effective amount of a compound according to claim 15, sufficient to inhibit the activation of the PTH2 receptor of said patient.

38. A method according to claim 30 wherein said medical disorder is abnormal CNS functions, abnormal pancreatic functions, divergence from normal mineral metabolism and homeostasis, male infertility, abnormal blood pressure or a hypothalamic disease.

39. A method according to claim 31 wherein said medical disorder is abnormal
5 CNS functions, abnormal pancreatic functions, divergence from normal mineral metabolism and homeostasis, male infertility, abnormal blood pressure or a hypothalamic disease.

40. A method according to claim 32 wherein said medical disorder is abnormal CNS functions, abnormal pancreatic functions, divergence from normal mineral metabolism and homeostasis, male infertility, abnormal blood pressure or a hypothalamic disease.

10 41. A method according to claim 33 wherein said medical disorder is abnormal CNS functions, abnormal pancreatic functions, divergence from normal mineral metabolism and homeostasis, male infertility, abnormal blood pressure or a hypothalamic disease.

42. A method according to claim 34 wherein said medical disorder is abnormal
15 CNS functions, abnormal pancreatic functions, divergence from normal mineral metabolism and homeostasis, male infertility, abnormal blood pressure or a hypothalamic disease.

43. A method according to claim 35 wherein said medical disorder is abnormal CNS functions, abnormal pancreatic functions, divergence from normal mineral metabolism and homeostasis, male infertility, abnormal blood pressure or a hypothalamic disease.

44. A method according to claim 36 wherein said medical disorder is abnormal
20 CNS functions, abnormal pancreatic functions, divergence from normal mineral metabolism and homeostasis, male infertility, abnormal blood pressure or a hypothalamic disease.

45. A method according to claim 37 wherein said medical disorder is abnormal CNS functions, abnormal pancreatic functions, divergence from normal mineral metabolism and homeostasis, male infertility, abnormal blood pressure or a hypothalamic disease.

25 46. A method of treating a medical disorder that results from altered or excessive action of the PTH2 receptor, which comprises administering to a patient in need thereof an effective amount of a PTH analogue or a truncated PTH analogue or a pharmaceutically acceptable salt thereof according to claim 1, sufficient to inhibit the activation of the PTH2 receptor of said patient.

30 47. A method according to claim 46 wherein said medical disorder is abnormal CNS functions, abnormal pancreatic functions, divergence from normal mineral metabolism and homeostasis, male infertility, abnormal blood pressure or a hypothalamic disease.

ABSTRACT

This invention relates to a series of PTH and PTHrP analogues that selectively bind to PTH2 receptors and as such may be useful in treating abnormal CNS functions; abnormal pancreatic functions; divergence from normal mineral metabolism and homeostasis, male infertility, regulation of abnormal blood pressure; and hypothalamic disease.

100 101 102 103 104 105 106 107 108 109 110 111 112 113 114 115 116 117 118 119 120 121 122 123 124 125 126 127 128 129 130 131 132 133 134 135 136 137 138 139 140 141 142 143 144 145 146 147 148 149 150 151 152 153 154 155 156 157 158 159 160 161 162 163 164 165 166 167 168 169 170 171 172 173 174 175 176 177 178 179 180 181 182 183 184 185 186 187 188 189 190 191 192 193 194 195 196 197 198 199 200 201 202 203 204 205 206 207 208 209 210 211 212 213 214 215 216 217 218 219 220 221 222 223 224 225 226 227 228 229 230 231 232 233 234 235 236 237 238 239 240 241 242 243 244 245 246 247 248 249 250 251 252 253 254 255 256 257 258 259 260 261 262 263 264 265 266 267 268 269 270 271 272 273 274 275 276 277 278 279 280 281 282 283 284 285 286 287 288 289 290 291 292 293 294 295 296 297 298 299 300 301 302 303 304 305 306 307 308 309 310 311 312 313 314 315 316 317 318 319 320 321 322 323 324 325 326 327 328 329 330 331 332 333 334 335 336 337 338 339 340 341 342 343 344 345 346 347 348 349 350 351 352 353 354 355 356 357 358 359 360 361 362 363 364 365 366 367 368 369 370 371 372 373 374 375 376 377 378 379 380 381 382 383 384 385 386 387 388 389 390 391 392 393 394 395 396 397 398 399 400 401 402 403 404 405 406 407 408 409 410 411 412 413 414 415 416 417 418 419 420 421 422 423 424 425 426 427 428 429 430 431 432 433 434 435 436 437 438 439 440 441 442 443 444 445 446 447 448 449 450 451 452 453 454 455 456 457 458 459 460 461 462 463 464 465 466 467 468 469 470 471 472 473 474 475 476 477 478 479 480 481 482 483 484 485 486 487 488 489 490 491 492 493 494 495 496 497 498 499 500 501 502 503 504 505 506 507 508 509 510 511 512 513 514 515 516 517 518 519 520 521 522 523 524 525 526 527 528 529 530 531 532 533 534 535 536 537 538 539 540 541 542 543 544 545 546 547 548 549 550 551 552 553 554 555 556 557 558 559 560 561 562 563 564 565 566 567 568 569 570 571 572 573 574 575 576 577 578 579 580 581 582 583 584 585 586 587 588 589 590 591 592 593 594 595 596 597 598 599 600 601 602 603 604 605 606 607 608 609 610 611 612 613 614 615 616 617 618 619 620 621 622 623 624 625 626 627 628 629 630 631 632 633 634 635 636 637 638 639 640 641 642 643 644 645 646 647 648 649 650 651 652 653 654 655 656 657 658 659 660 661 662 663 664 665 666 667 668 669 670 671 672 673 674 675 676 677 678 679 680 681 682 683 684 685 686 687 688 689 690 691 692 693 694 695 696 697 698 699 700 701 702 703 704 705 706 707 708 709 710 711 712 713 714 715 716 717 718 719 720 721 722 723 724 725 726 727 728 729 730 731 732 733 734 735 736 737 738 739 740 741 742 743 744 745 746 747 748 749 750 751 752 753 754 755 756 757 758 759 760 761 762 763 764 765 766 767 768 769 770 771 772 773 774 775 776 777 778 779 780 781 782 783 784 785 786 787 788 789 790 791 792 793 794 795 796 797 798 799 800 801 802 803 804 805 806 807 808 809 810 811 812 813 814 815 816 817 818 819 820 821 822 823 824 825 826 827 828 829 830 831 832 833 834 835 836 837 838 839 840 841 842 843 844 845 846 847 848 849 850 851 852 853 854 855 856 857 858 859 860 861 862 863 864 865 866 867 868 869 870 871 872 873 874 875 876 877 878 879 880 881 882 883 884 885 886 887 888 889 890 891 892 893 894 895 896 897 898 899 900 901 902 903 904 905 906 907 908 909 910 911 912 913 914 915 916 917 918 919 920 921 922 923 924 925 926 927 928 929 930 931 932 933 934 935 936 937 938 939 940 941 942 943 944 945 946 947 948 949 950 951 952 953 954 955 956 957 958 959 960 961 962 963 964 965 966 967 968 969 970 971 972 973 974 975 976 977 978 979 980 981 982 983 984 985 986 987 988 989 990 991 992 993 994 995 996 997 998 999 1000

Docket No.

BPC073

Declaration and Power of Attorney For Patent Application

English Language Declaration

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

PTH2 Receptor Selective Compounds

the specification of which

(check one)

☒ is attached hereto.

☐ was filed on _____ as United States Application No. or PCT International Application Number _____ and was amended on _____ (if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)

Priority Not Claimed

(Number)

(Country)

(Day/Month/Year Filed)

☐

(Number)

(Country)

(Day/Month/Year Filed)

☐

(Number)

(Country)

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I hereby claim the benefit under 35 U.S.C. Section 119(e) of any United States provisional application(s) listed below:

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(Status)
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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. *(list name and registration number)*

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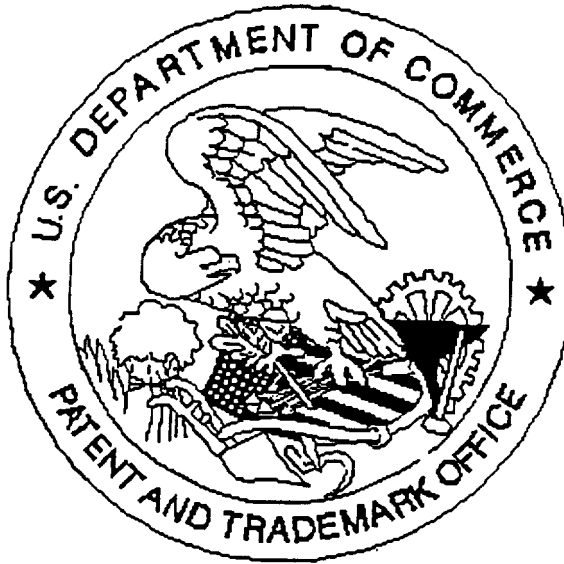
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Fourth inventor's signature	Date
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Fifth inventor's signature	Date
Residence	
Citizenship	
Post Office Address	

Full name of sixth inventor, if any	
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